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Proceedings of the 44th Annual Scientific Meeting

The Committee on Problems of Drug Dependence, Inc.

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Problems of Drug Dependence, 1982

Proceedings of the 44th Annual Scientific Meeting,
The Committee on Problems of Drug Dependence, Inc.

Editor, Louis S. Harris, Ph.D.

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Foreword

The Proceedings of each Annual Scientific Meeting of the Committee on Problems of Drug Dependence (CPDD) comprise a kind of contour map of one year's explorations and advances along the frontiers of our knowledge about drug abuse. The remarkably broad range of research interests among the membership of the CPDD is reflected in the record of its meetings and the expertise of its membership, which includes biochemists and pharmacologists, physicians, sociologists, psychologists and other public health professionals. The proceedings of its annual meeting enable the reader to consider the vast scientific territory of recent research advances in substance abuse in a single volume. For that reason, the National Institute on Drug Abuse is once again pleased to publish the CPDD proceedings in its Research Monograph series.

As in past years this volume contains a variety of timely papers and progress reports on ongoing investigations in the field as well as the annual report of the CPDD Drug Testing Program which evaluates the efficacy and dependence liability of new compounds. Several of the papers from the 44th Annual Scientific Meeting, held in Toronto on June 27-30, 1982, present Canadian perspectives on issues of common concern.

Approximately half of the projects discussed are fully or partially supported by NIDA but much work is also underwritten by our sister Institutes in ADAMHA, by other Federal agencies, by State governments, by the governments of other countries, and by private industry. A most important contribution of the CPDD is its linking of the efforts of all of these groups to enlarge our understanding of psychoactive substances and their effects on human health and behaviors. This should help lead toward more effective prevention and treatment of the serious public health consequences of drug abuse.

William Pollin, M.D.
Director
National Institute on Drug Abuse

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The J. Michael Morrison Award, 1982

Robert C. Petersen

One rarely gets ten minutes to say just about anything one wishes, to as distinguished an audience as this. But, since Joe Cochin assures me I can, I mean to take full advantage of it.

To say that I feel honored and grateful to be the first recipient of the J. Michael Morrison Award is to belabor the obvious.

When I first joined Roger Meyer, then Acting Chief of the newly formed Center for Studies of Narcotics and Drug Abuse, I had no idea that so much of my professional life would become involved in drug abuse. Actually, I was more interested in mind alteration more generally, with drug use as only one aspect. But the Center, with Roger as its energetic chief, seemed like an interesting place to pursue my interests. What a small handful of professionals supported by a committed staff we were -- and with responsibility for prevention, treatment and research all in a highly visible area. Fortunately, the sheer magnitude of the newly passed NARA* program was so obviously overwhelming that NIMH, of which we were a part, created a Division of Narcotics and Drug Abuse. That relieved us of the treatment aspects, freeing us to focus on research which was of more primary interest. Nevertheless, I remember Roger Meyer, who was surely dynamic, eagerly awaiting his discharge from the Public Health Service while muttering darkly that if he had to remain Chief much longer he would climb the walls! Unfortunately, the plane from California was slow, the Washington scene dynamic, and by the time Sid arrived he discovered he was slated to become Division Director. More or less by default -- there being no more obvious contenders -- I inherited Sid's mantle. How often I wished in succeeding months I could return it!

It was a hectic time -- to say the least, a challenging time. Marijuana, LSD and amphetamine use were all burgeoning. Public concern approached hysteria and our program had high priority. That does not, of course, mean that we had anything but the most general ideas of just how to set up such a program. While there were distinguished researchers in a few places, such as the Addiction Research Center in Lexington, it's safe to say that more traditional research settings, such as universities, were not overly eager to become involved in drug research that might bring them notoriety. Moreover, the Federal Bureau of Narcotics and

*Narcotic Addict Rehabilitation Act

Dangerous Drugs was a mite suspicious of the motives of those eager to become involved, especially in marijuana research. Even the well specified natural and synthetic materials needed for orderly pharmacological research were largely unavailable. Development of such resources was viewed with restrained enthusiasm by the general public. Creation of a marijuana "plantation" at the University of Mississippi, thought humorous by some, was greeted with downright indignation by others. I remember a long distance call from a lady representing the Garden Clubs of America. She demanded to know why we were "wasting" $60,000 of the taxpayer's money when the ladies of her garden clubs would be happy to grow the needed material as a public service. My explanation of the need for uniform growing conditions and adequate security left her unimpressed. She assured me that the good ladies would not dream of diverting the pot to their personal use. It was only when I explained that the ladies were not the problem, but unspecified others who might steal the plants, that she was somewhat mollified. And, of course, there were the inevitable letters from farmers who wanted to get in on the ground floor of the government's new "support" program.

Letters from the general public ranged from the sensible to the sometimes bizarre and unconsciously humorous. I regret that we didn't keep a scrapbook of some of them. But all had to be answered -- together with congressional inquiries -- while planning an overall program. We certainly had our hands full on many fronts. Thinking back to our beginnings, there were those who richly deserved to be honored, but only rarely were. One of them was certainly Eleanor Carroll whom some of you remember as vividly as I. I doubt that anyone who ever encountered her failed to remember her very vividly. Ellie, while technically a sociologist, was very widely read, formidably bright, immensely dedicated, and not a little intolerant of bureaucratic absurdity. She surely did not "suffer fools gladly."

In her uncompromising pursuit of excellence she shaped our overseas program, most of our psychosocial research program, and her colleagues as well! Although she could be as kind as she could be critical, few -- including those on the highest echelons -- were eager to be confronted by her. They would often go out of their way to avoid having to explain a bureaucratic decision they knew she viewed with a jaundiced eye. Ellie could chill the soul of the hardiest administrator, were she to make her dismay visibly apparent in a meeting, by rolling her eyes or striking her forehead in evident distress at the administrator's remarks. I'll only tell one Ellie story, although they are many. During a research review committee or IRG meeting, Ellie became increasingly irritated with a reviewer who alluded to the physical attributes of a woman P.I. Unable to contain herself any longer, Ellie roared -- in Spanish -- that the next time she went on a site visit to a male P.I., she intended to include in her review that he had "testicles the size of a cathedral." Following her Spanish version, she offered her own inimitable translation for the uninitiated. Needless to say, the frequency of remarks alluding to the physical attributes

of our principal investigators dramatically decreased. There were many impressive members of our initial review groups as well, some of whom are here today. I hesitate to single any out for surely I would omit others no less impressive. But, I would especially like to mention Jack O'Donnell of the Addiction Research Center. To the very end of his very productive life Jack gave generously of his time, his energy, and his wisdom in shaping our program. Whatever the request -- to consult, make a site visit or to write a report -- Jack rarely refused and always gave in full measure. Then, as now, review committee members were overworked, underpaid, and their contribution largely unrecognized. While peer review has its problems, in my opinion, it is like democratic government itself, the best system so far devised.

I would, most especially, like to thank all those who served on review committees during my tenure who gave so freely of their wisdom and time to help make our programs work.

During my years as Center Chief at NIMH, I increasingly chafed at the role of being an administrator. As the organization grew inevitably larger and the bureaucratic restrictions multiplied, more and more energy seemed to be consumed overcoming the inertia of the cumbersome bureaucracy. The yeasty initial excitement of innovative programming became increasingly an ordeal of meeting a myriad of requirements that often seemed extraordinarily remote from accomplishing our objectives. I had long cherished the idea of developing a Research Monograph Series of high quality to provide integrative reviews of our scientific knowledge concerning drug abuse. I also yearned for the opportunity to once again play a planning role, to supplant the "go, go, go" demands with which we were contending daily with more thinking. Our reorganization as part of NIDA provided an obvious opportunity to realize these long dormant objectives. Fortunately, NIDA's new research director, Bill Pollin, shared the vision. "Thank you, Bill, for your support."

Once again, a formidable woman entered my life. Her name was Eunice Corfman. I had talked with a number of people who might assist in editing the new Research Monograph Series without much conviction that any of them really suited. Bill Pollin suggested I might want to talk with Eunice. Within the first ten minutes I was convinced she was the person for the job. While her background in science was modest, her commitment to learning about it was not -- and she was impressively bright. Whether the question was one of readability of possible format or actual content, Eunice was soon knowledgeable. Not easily daunted, her energies seemed limitless and through our combined efforts the new monograph series was launched. Alas, as was true of others hired, one hazard of hiring very able people is that they are soon offered still more demanding opportunities elsewhere. It was, however, a shock to us all when shortly after becoming publications chief at NIMH Eunice died quite suddenly. I'd like to take this opportunity to publicly thank her for her profound contribution to my life, both professionally and personally.

Looking back -- as well as looking forward -- is especially rewarding after having retired from government service at a relatively young age. I did not start out to be a bureaucrat, but I soon discovered that without bright, committed bureaucrats, the pursuit of excellence in the larger scientific community is far more difficult, and sometimes impossible. Michael Morrison typified the best in that type of commitment. Unlike the stereotyped government worker more interested in his paycheck than his performance, Michael pursued his task with impressive courage and dedication to the end of his tragically short life. I am very proud to be chosen as exemplifying the tradition of scientific administration and service that Michael Morrison represented.

This is a difficult time for many in government service. Too often their contribution is minimized and there has been the implication that their jobs are sinecures. Any of us who have navigated the bureaucratic straits in pursuit of excellence know just how false that characterization is. It has been my privilege to have worked with some of the ablest and the best. Without their collective dedication, an innovative program of the proportions that has resulted would not have been possible. To have been involved from a program's inception to its initial fruition -- and to have that role recognized -- is gratifying, indeed. There have certainly been times of profound self doubt in which I wondered whether my choice of government service was a worthwhile career choice. This is not one of them.

Thank you all.

Author

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Pharmacological Treatment of Narcotic Addiction (The Eighth Nathan B. Eddy Memorial Award Lecture)

Vincent P. Dole and Marie E. Nyswander

Marie and I are privileged to join with you in honoring the memory of Nathan B. Eddy. We owe much to him. On two critical occasions, he endorsed our efforts when it appeared that the work might be stopped by unfriendly authorities.

In 1955, eight years before I knew her, Marie Nyswander presented a paper before this Committee suggesting that narcotic addicts could be treated on a voluntary basis as ambulatory drug-free patients by psychotherapists in New York City. Although this approach was totally at odds with the accepted practice of incarceration and compulsory treatment and had been condemned by the Federal Bureau of Narcotics, the Committee listened sympathetically and encouraged her to go forward with the trial. She recruited physicians, psychologists and social workers to work as unpaid volunteers in this project, and carried it through to a conclusion.

Three important findings came from this pilot study: chronic users of heroin were found to be sufficiently motivated to volunteer for treatment; they did not present any exceptional problems in management as medical patients; and psychotherapy with social support was not an adequate treatment for persons with longstanding habits of daily heroin use. In short, she established that heroin addicts could be considered as persons with a chronic disease for which an effective medical treatment remained to be discovered. This pointed to the next step when I joined her in 1964. We decided to look more closely at the functional state of long term addicts given controlled doses of various narcotic drugs under non-punitive conditions. After much preliminary planning and with support from various authorities including Dr. Eddy, we began the research on a metabolic ward of Rockefeller University Hospital.

It soon became apparent that methadone, when given in a constant daily dose, had functional effects quite different from those of injected heroin, morphine, and other usual narcotics. Patients on stabilized doses of methadone lost their craving for narcotics and appeared functionally normal in all important respects. They were able to return to their old neighborhoods without being drawn back

to heroin. They re-established family structures, attended school, obtained jobs and desisted from criminal activities. At the time we were unable to explain the marked difference between methadone and heroin, but accepted it empirically as a basis for a rehabilitation program.

Not long after this study had begun we were asked by Dr. Eddy to summarize our findings before this Committee, which we did in the annual meeting of 1966. Fortunately we had documented the work in great detail. To provide an objective measure of drug taking, we introduced a routine of daily urine testing after adapting a chromatographic method of Joseph Cochin for large scale use. We established a computerized data system to record the intake and discharge of every patient who entered treatment, including even those who remained for no more than one day. We initiated systematic studies of coordination, intellectual function and vigilance. We established job placement services and legal supports to help in rehabilitation and to record the shift from criminality to normal social functioning. We invited experts in pharmacology and social services to visit our clinic and interview our patients.

The Committee appeared to be favorably impressed by these results. It encouraged us to continue, while emphasizing that the treatment was still in a research stage needing further systematic study. At the time we did not fully realize how fortunate we were in receiving this endorsement. Some years later, when reading Eddy's monograph in the work of this Committee, we learned that the Bureau of Narcotics had been looking for scientific justification to extinguish the study. Without the endorsement given to us at this critical time by the leading scientific authorities in the field, our work probably would have been terminated and the effort recorded in history as another failure of maintenance treatment. My admiration for Dr. Eddy's scientific integrity was heightened by his frank comment that he personally disliked the idea of giving any narcotic drug to addicts, and felt that it should be possible to discover a better way of treatment - but that, nevertheless, he supported the work as scientifically competent research. During the subsequent sixteen years, mindful of his rigorous standards, we have been reaching for a biochemical understanding of maintenance treatment. We wish that he were here with us today to discuss the matter, taking into account modern discoveries of endogenous opioid peptides and further evidence supporting the metabolic disease concept of narcotic addiction. In default of this opportunity, we address our report to his successors, as surely he would have wanted us to do.

Our hypothesis of narcotic addiction as a metabolic disease stemmed from the consistent therapeutic response of chronic, previously intractable, addicts to adequate doses of methadone. Normalization of function occurred independently of social status, age, ethnic classification and personality type. It suggested to us that the medication was somehow correcting (or compensating for) a biochemical defect which was expressed in an abnormal appetite for narcotic drugs. In 1967, we therefore launched a search for stereospecific binding sites in the brain of rats, using radio-labeled l- and d- methadone.

The study failed to disclose any, but in analyzing the reasons for our failure it became obvious to us that the discovery of specific narcotic binding sites would require narcotic ligands of higher specific activity and higher radiochemical purity than any available at that time. This finding was reported in 1970. Subsequent work in other laboratories substantiated this interpretation and carried the work far beyond our simple expectations.

Meanwhile in pursuing the difference between chronic administration of heroin and methadone we obtained an explanation of why methadone, but not heroin, can sustain patients in normal function. Reversible binding of methadone by tissues in the liver and elsewhere establishes a huge buffer of inactive drug that stabilizes the blood level. As circulating methadone is removed by metabolism, it is replaced by dissociation of molecules from non-specific binding sites in the tissue. The difference in clinical effects of methadone and other narcotics therefore does not reflect differences in action at the stereo-specific binding sites; it is simply a reflection of the much slower clearance of methadone from the blood.

When one compares the clinical phenomena of euphoria and abstinence in addicts with the blood levels of narcotic drug, the quantitative association between biochemistry and behavior becomes quite clear. Figures 1 and 2 show (schematically) the disparate effects of heroin and methadone in a narcotic addict and a maintenance patient, respectively. Both individuals have been made physically dependent by repeated administration of a narcotic drug, and therefore will experience withdrawal symptoms if the concentration of circulating drug falls below a critical level. At the upper limit, both are pharmacologically tolerant and thus are protected from disabling narcotic effects until the circulating concentration is quite high. Here the similarity ends, because blood morphine (the active metabolite of heroin) fluctuates rapidly between the extremes of narcosis and abstinence, while methadone remains relatively constant if the medicine is given in proper dose on a fixed schedule. The reservoir of bound methadone stabilizes the concentration of blood in circulation, and possibly releases extra drug under conditions of stress.

What we are witnessing in clinical symptomology is a titration of narcotic receptors in the intact organism using the clinical state as an end point. From this perspective it is interesting to note that the apparent binding affinity of these receptors *in vivo* is 1 or 2 orders of magnitude lower than the μ receptors that have been studied *in vitro*. Either the functionally significant receptors are of a category still undiscovered, or more likely the affinity of receptors *in vivo* is modulated downward by local conditions of temperature, salt concentration and competitive ligands. Since the addict can be normalized by exogenous narcotic, it seems unlikely that the defect in addiction is a failure of transducer function of the narcotic receptors. As a speculation, we suggest that the link between biochemistry and addiction will be found in deficient production of endogenous opioids, impaired release of these ligands in stress, or in abnormally low affinity of receptors. These variables are open to study with modifications of existing methods. If our

speculation is correct, the deficiency in endogenous opioid function will provide a rationale for maintenance treatment that would meet even the rigorous criteria of Nathan Eddy. Incidentally, according to this interpretation naltrexone and other narcotic antagonists are precisely the wrong agents to use in treatment of narcotic addiction. If endogenous opioids are deficient, antagonists would add to the biochemical disability. Their therapeutic efficacy, in comparison to that of agonists, thus provides another test of the metabolic theory of addiction.

Before closing, let us leave no doubt that this award reflects the efforts of many hundreds of quietly dedicated people. We have been fortunate in our associates. While it is impossible to list all of them, at least we must note those who contributed in the early, formative stage of the work: Beatrice Berle pioneered in the delivery of medical services in Harlem and introduced Marie Nyswander to work in this area. Mary Jeanne Kreek participated in the studies of narcotic pharmacology, and has emerged as a leading authority in this field. Joyce Lowinson, Harold Trigg,and Robert Newman participated in the clinical application, and showed the feasibility of large-scale treatment programs. Norman Gordon and Ann Ho demonstrated the functional normality of stabilized patients using sophisticated tests of coordination and reaction time. Ray Trussell, as an administrative leader in public health, lifted us out of the sheltered world of metabolic research and enabled us to develop maintenance programs in the context of a general hospital. The Trustees of Beth Israel Medical Center were courageous in their firm support of this program at a time when it was surrounded with controversy. And, above all, the addicts themselves, with the sad wisdom of their experience, guided our efforts. We proudly accept this distinguished award on behalf of these contributors.

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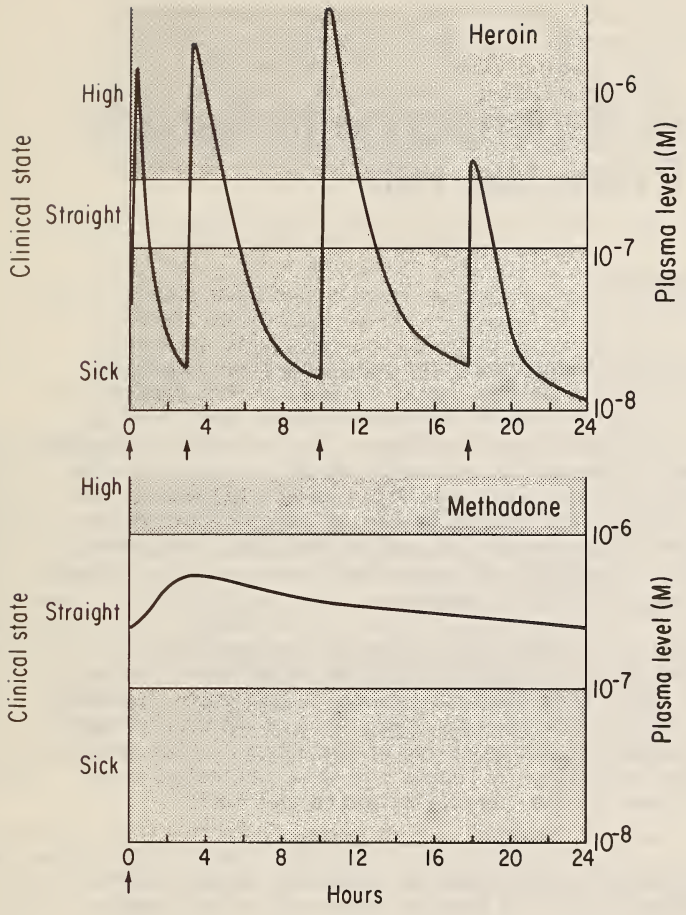

FIGURES 1 and 2. The essential difference between methadone maintenance and chronic use of heroin is illustrated in these schematic diagrams. A maintenance patient can be stabilized on a constant dose of methadone, which holds the blood level in the range of normal function. The heroin user is repeatedly disabled by alternating periods of narcotic effect ("HIGH") and abstinence ("SICK"), even with multiple injections during a 24-hour period. Because of instability of the blood level of morphine (the metabolite of heroin) and the need for progressively increasing doses, "heroin maintenance" fails as a treatment program. In contrast, patients remain in good health and normal function for years when maintained on a constant daily dose of methadone.

Chemical Dependence in Canada: A View From the Hill

Ian W. D. Henderson

While Canada has not been immune for many years to substance abuse, it is recently that the social as well as the health aspects of the non-medical use of drugs have been recognized as causative of a multiplicity of problems. It is generally agreed that the largest component of substance abuse in Canada still rests with the simple chemical ethanol. We are all aware, however, that the social and addictive use of psychotropic drugs cannot be ignored from the public health viewpoint, and that many adverse social effects are engendered as a result of abuse of a wide variety of chemical agents.

It was well stated in A New Perspective on the Health of Canadians, issued by Marc Lalonde, Minister of National Health and Welfare in 1974, that there are risks of all sorts inherent in drug use, and that for the most part, all of these are self-imposed. The effect of drug-related risk-taking on the levels of sickness and mortality in Canada is well reflected in a delineation of destructive lifestyle habits and their consequences.

(a) alcohol addiction leads to cirrhosis of the liver, encephalopathy and various forms of malnutrition;

(b) social excess of alcohol leads to a very high incidence of motor vehicle accidents, which account for a very high proportion of premature deaths among young people of both sexes in Canada;

(c) cigarette smoking causes chronic bronchitis, emphysema and cancer of the lung; at the same time, it aggravates coronary artery disease;

(d) the abuse of pharmaceutical agents of legal origin not infrequently results in states of drug dependence, and occasions a variety of drug adverse reactions and interactions. It was for this reason that Canada in 1972 chose to restrict drastically the conditions for which amphetamines could legally be prescribed; it is also this which expedites our examination on a regular basis of the scheduling of drugs to groups that require appropriate degrees of social and professional control in terms of general availability;

(e) other psychotropic drugs lead to suicide, homicide, and to many forms of accidents;

(f) the continued and regular social use of a variety of mind-altering drugs leads to social withdrawal, "anomie", alienation, nonproductivity, and to acute panic and anxiety states that commonly require expert treatment.

Notwithstanding this holistic approach, one can readily contend that in terms of drug-related crime, and the cost to society, opiate abuse is unique. Although it is difficult to provide definite figures concerning the prevalence of addictive states when the substances involved are legally prohibited, it appears that within Canada's presumed 15,000 heroin-dependent persons, the number of convictions for possession or trafficking represents only 5%; in terms of the total number of heroin users, both dependent and nondependent, the conviction figure represents under 1% of the true numbers involved. The conviction rate, therefore, is little more than the tip of an iceberg which warns us of the vast nature of this drug problem in our country - a problem which is relatively hidden from view of the general public.

The policy of government against heroin addicts in Canada has been one of containment. Our police forces have had to attempt to apprehend the opiate user when he has prepared the substance for use, and when he is just about to use it. This apprehension has been predicated by the need to possess a sample of the substance before it is placed beyond physical reach. In this sense, possession "in the hand" and possession in some physiological compartment of the body are not regarded by the law as entirely equivalent. A high proportion of persons convicted of possession of opiate narcotics have previous criminal records. Federal penetentiaries demonstrate an average of over 8 convictions per person. These previous offences usually include breaking and entering, theft, forgery, counterfeiting, possession of stolen property, vagrancy and prostitution. There are also many kinds of violence.

The situation in terms of alcohol is entirely different. While it is true that alcohol is associated with a number of types of crime, including personal assault and rape, impaired driving, theft, brawling, wife and child abuse, and homicide, it is relatively infrequent that people who are alcohol dependent are in deliberate contravention of the law. This is due to the fact that ethanol is entirely legal and is usually bought in a legal manner, rather than obtained by theft. The vast majority of alcohol-dependent persons in need of treatment are not skid-row alcoholics, but persons whose only transgressions are those of social disintegration and personal health deterioration.

If substance dependence states, whether these be opiate, barbiturate, or alcohol related, are to continue to be regarded in Canada as "treatable conditions," then individuals with any of them must be included under the heading of persons whose drug-induced states warrant subsidized care, treatment and rehabilitation. Apart from actual medical treatment of the many conditions that can result from substance abuse, there are social forms of treatment including retraining, job placement, sheltered workshops, and a slow build-up of self-esteem and feelings of personal social responsibility.

You realize that there are many basic issues with respect to control of drug abusers. These include relevant and pertinent questions regarding: the appropriateness of offences for simple possession; offences for non-medical use, both intermittent and regular; what the penalties for such offences ought to be; and whether there should be coercion or compulsion for treatment with respect to the users.

Despite continuing concern over the social limitations and the social consequences of employing a form of criminal justice in the field of non-medical drug use, the majority of law-abiding citizens in Canada are greatly concerned with crime in our society, and they are constantly asking about the relationship of this crime rate to the abuse of drugs. There is moreover a growing public concern over wasted lives and the societal problems that are created by chronically dependent persons. This is particularly relevant for the heroin addict who must commit criminal acts to survive in his dependent state. It is perhaps less an issue with regard to the cocaine user, who is not uncommonly a relatively affluent, if not wholly respectable, member of the social community. The LeDain Commissioners in their final report discussed the controversy that underlines the case for coercion or mandatory treatment of the drug addict. Some Canadian experts have argued against the assumption that persons can be motivated for treatment by any form of coercion; indeed some contend that any person who is compelled to submit to any form of treatment will almost invariably lack the

motivation which is essential to a successful outcome. There is almost certainly some merit to this argument, but I am not sure that it is universally the case.

Even although actual apprehension has been caused by drug-related criminal behaviour such as theft, it is probably not essential that all offenders have to be subjected to confinement. For some, adequate control can be exercised within the community by means of surveillance in the form of parole or probation, or within community programs. However, non-confinement treatment is very difficult to accomplish in view of the small number of probationary officers, their very large work loads, and their general lack of enthusiasm for this type of work. It is difficult to launch and maintain non-residential programs unless adequate training facilities for professionals and para-professionals are available, and unless continuing community support is forthcoming. Again, any form of community control of the drug abuser has to be backed up by some sanctions for violations of the conditions of the probationary form of "court-diversion" from a confinement in prison. Probably the only effective sanction is the deprivation of liberty. If we in Canada choose a system of control of the drug user, it will be necessary to prepare ourselves for the use of some forms of confinement. If this is so, then it is obvious that we must possess both the facilities and the will to make the threat of confinement a credible back-up position. Confinement as such however is unlikely to accomplish any therapeutic goal. Treatment, therefore, in a residential setting has to be regarded in a totally different light from programs for non-motivated incarcerated addicts. The therapeutic community has obviously been developed to fill this gap. What has still to be established in Canada is a formalisation of court diversion from punition to treatment - be that residential or not.

JURISDICTION IN CANADA WITH RESPECT TO HEALTH

There have been expressions of opinion that the general or residuary jurisdiction with respect to health rests with the Parliament of Canada on the basis of its general power; but the weight of opinion and the assumption on which governments have been acting, is that the provision of health care rests with the provinces. Parliament, of course, can invoke its general power to cope with emergencies. Two important functions in respect to health are treatment and quarantine. In each case, the general jurisdiction appears to be provincial. The primary jurisdiction with respect to medical treatment lay with the provinces by virtue of Section 92(7) of the British North American Act, which conferred upon provincial legislatures exclusive jurisdiction with respect to "the establishment, maintenance and the management of hospitals, asylums, charities and eleemosynary

(sic) institutions in and for the province, other than marine hospitals." The federal jurisdiction with respect to the establishment of treatment facilities was also restricted. The only expressed power was in Section 91(11), which gave Parliament jurisdiction with respect to "quarantine and the establishment and maintenance of marine hospitals." In addition, Parliament may establish and manage treatment facilities in other areas of Federal concern such as the Armed Forces, the Indian population on reservations, the population in federal institutions, and in matters of health related to immigration.

It is necessary to distinguish between the regulatory jurisdiction with respect to hospitals and other treatment facilities which lies with the provinces, and capacity of the Federal Government through the exercise of its spending power to provide financial assistance for the establishment of facilities within provinces. The use of the Federal spending power in areas beyond Federal legislative jurisdiction remains a controversial issue as a matter of policy, but it has not ever been ruled to be constitutionally invalid. By this device, the Federal Government may impose conditions upon grants of financial assistance, which will assure the implementation of certain Federal policies and standards.

Whether the Federal Government has a true general power in relation to non-medical drug use, and the scope of that federal power with respect to matters of health are particularly relevant in view of the non-penal dispositional alternatives suggested by Article 22 of the Convention on Psychotropic Substances (1971), which provides

> . . . when abusers of psychotropic substances have committed such offences, the parties may provide, either as an alternative to conviction or punishment, or in addition to punishment, that such abusers undergo measures of treatment, education, after-care, rehabilitation and social re-integration in conformity with Paragraph 1 of Article 20 . . .

I should, of course, point out that Canada is not yet a signatory to this Treaty but probably will be in the not too distant future.

In the absence of a true general power with respect to non-medical drug use, or a general jurisdiction with respect to health, federal powers to provide for treatment have to be grounded on the Criminal Law. On this issue, the special committee of the Senate on the traffic in narcotic drugs which reported in 1955, contended:

> . . . that it is not within the constitutional authority of the Federal Government to assume responsibility for treatment of drug addicts, nor to enact the kind of legislation necessary in that connection. This legislation would need to include the compulsory treatment of addiction, the legal supervision of control over the individual during treatment, and the right of control of the individual following treatment to prevent his return to the use of drugs, former associations or habits. These are considered to be matters beyond the competence of the Federal Government.

Notwithstanding, Parliament has provided for the compulsory treatment of drug offenders in Part II of the Narcotic Control Act (1961). However, this part of the Act has not yet been put into force by proclamation. This may be so because of doubts about the constitutional validity of these provisions, or the failure to develop suitable treatment methods and facilities, or, in fact, the continuing reservations of the Federal Government as to the advisability of compulsory treatment in principle, or a combination of all these.

For this reason, facilities necessary for the acceptance from the courts of drug offenders, whose offence has been occasioned by their state of dependence or addiction, have been very few in number. This is in contrast with the United States, where residential facilities, including therapeutic communities, receive a considerable proportion of their clientele from the law courts as a form of diversion to treatment in lieu of punishment. In France since 1970, the illicit use of drugs has been an offence. Provided that persons are charged and convicted of the offence, they may be ordered by law enforcement authorities to submit to detoxification, following which they can be kept under medical surveillance for indefinite periods of time.

Canadian experience, however, with the deprivation of liberty as a means of facilitating treatment and rehabilitation has so far not been encouraging. Treatment within prison settings has been unsatisfactory. Indeed, bringing addicts together for long periods of confinement without a restructuring of lifestyle accomplishes little or nothing. It may indeed have a negative effect.

TREATMENT NEEDS OF DRUG ABUSERS

While there are many physical needs of many drug abusers, there is a proportion within any sample of narcotic-addicted persons who need some form of what is generically referred to as psychotherapy. Often it is this group that voluntarily seeks aid for their problems that are commonly long-standing in nature.

The therapeutic community, the history of which is well documented, was predicated on the concept that a controlled environment could be utilized as an effective instrument of therapy. The idea is not a new one; indeed nearly all theories of personality development have emphasized the fundamental importance of inter-personal relationships, group experiences and social interactions. Nevertheless, in spite of this awareness and notwithstanding its historical and basic importance for all behavioural sciences, the therapeutic community has been poorly appreciated in the treatment and the rehabilitation of both drug and alcohol abusers.

This might be due to the relative newness of the term, which originated with Maxwell Jones about 25 years ago. Another factor may be the wide disparity of standards that have existed in North America among various therapeutic communities. Some have been based in schools, others in prisons, and others within community or half-way houses. They have ranged from crisis intervention centers to long-term residential facilities. Some have tolerated a code of behaviour that has been generally unacceptable to the community at large, while others have enforced strict, demanding codes of conduct. Starting patterns have varied from purely professional to entirely non-professional. Some programs have maintained liaison with the establishment, the law enforcement agencies, and the courts, while others have eschewed this entirely. There are programs, the orientation of which is to return persons to society as constructive, productive citizens, while others have held that society itself is the villain, and it may be counterproductive for residents ever to consider leaving the umbrella of group support.

Approximately six years ago, I was privileged to receive a special award from the National Institute of Drug Abuse of the United States to join a group of drug dependence administrators from overseas countries in examining American programs in a number of large U.S. cities. During that month-long stay, I saw for myself how many differences exist within various modifications of the models of treatment.

There is, however, a general sense of agreement for an existential approach on the basis of three principles:

1. addicts are curable until proven otherwise;

2. that they are, and should be treated as though they are responsible for their own conduct and treatment;

3. that the treatments must be aimed at profound character reconstruction, rather than just physical detoxification and social adjustment.

In virtually all the programs that I was privileged to visit, there was the belief that underlying all severe chronic drug use, there are serious maladaptive patterns of response to emotional states which are induced by biological needs and psychological conflicts, as well as by outer stress, familial, social and situational in nature. It appears to be generally accepted that such emotional response patterns predispose individuals to drug use. At the same time, there continues to be an optimism that these patterns can be altered. The primary objective, therefore, has to be the effective alteration of ineffective emotional and response pattern behaviours, to more effective ones.

I believe, personally, that there is still a place for the professional worker and the physician within most treatment programs, especially to identify possible psychopathology within the residential body. Serious and even irreparable damage can occur as a result of say, encounter technology when the fundamental distinction between the sociopath and the pre-psychotic is not wholly appreciated. While the sociopath improves as a result of healthy guilt feelings and stressful anxiety, these very techniques can be wholly destructive of the individual who has an underlying mental illness, such as undiagnosed depression.

I was especially interested to note that in some programs of the United States, there are special provisions for women. It seems clear that the needs of the pregnant addict, the older female and the addicted mother are often beyond what the average "co-educational" program can provide. It is even possible to contend that in addition to the emotional problems found in male addicts, females have additional problems of hostility, and a confused sexual identity, not uncommonly manifested with a degree of brutality. Most of them seem to have grown up in a sterile, unemotional milieu. Most seem never to have known what it is like to be loved, nor have they ever experienced any warm, meaningful relationships. Most have not been prepared to become adequates mothers. All this can lead to the birth of a child by a mother whose main motive in the pregnancy seems to be a re-assertion of her female ego. What is disturbing about this is the reported high incidence of child abuse and child neglect, directly attributable to drugs, or alcohol-addicted parents.

From a community perspective, it is becoming increasingly clear that for the highly complex field of treatment of addicted states, a multi-modality approach is required. Psychotherapy still has a place, albeit a small one; for others, some form of behaviour modification may be appropriate. Chemical aversion has its advocates, while contingent reinforcement is a better approach for others. Even acupuncture may be indicated for some!

If the Department of National Health and Welfare has any concern, it seems to rest on the tendency of many forms of treatment to substitute one kind of dependence for another. While this is not done in terms of one drug for another within therapeutic community programs, there is even the potential for dependence on the program and its specific principles. It is a feature of nearly all forms of chronic treatment, and even therapeutic communities cannot escape from it. It is a seductive trend which is easy to ignore, especially when one is intimately concerned with treatment, and may, in fact, be more obvious to an outsider than those involved with the program itself.

METHADONE PROGRAMS

While Canada has established both methadone slow withdrawal and methadone maintenance programs in all geographic areas that have a significant opiate problem, there has not been the enthusiasm for maintenance that has been reported from the U.S.A.

A publication from the Addiction Research Foundation of Toronto in 1972* analysed the outcomes of the first 90 patients treated within the methadone maintenance program. They reported that half of the male patients left the program voluntarily either by quitting without notice (28.1%) or by requesting a planned withdrawal (21.9%). A further major cause for dismissal from the program was legal arrest (37.5%) of the men and (31.6%) of the women. The most prominent cause of discharge among women was excessive drug use other than narcotics, involving most often barbiturates. About 16 months after the last patient intake it was found that over 50% of the group discharged voluntarily or by dismissal were readdicted to heroin or other narcotics. One in four was in prison.

In a study of employment rates the authors found that after one year on methadone maintenance 66.7% of their patients were working or participating in a vocational rehabilitation program. At the time that they entered the program 43.6% of the group was employed. This was considered a limited success.

With regard to employability of methadone-maintained persons it is generally accepted that one legitimate excuse which can be made by methadone program directors for limited success in this area is that they are being asked to attain levels of employment and productivity for people who, prior to their use of heroin, were chronically unemployable. Indeed, a high percentage of heroin users in their early 20's have little or no skills, a

* M. Krakowski; R.G. Smart: "The Outpatient Treatment of Heroin Addicts with Methadone." Can. J. Public Health, 63 (1972) 397-404.

limited education, and usually no established work pattern. A high proportion has never worked at all. It may be somewhat unfair therefore to expect methadone programs to accomplish a vocational reintegration process into society when the limited capabilities antedated, and were not the result of, heroin use.

In the year 1975 the Government carried out an investigation into the reasons for a decline in a number of Canadian addicts receiving methadone as part of their treatment of opiate addiction. Specifically program controls were examined with a view to establishing whether or not they were so stringent that they were discouraging new addict clients; and whether or not our controls, if lessened, would lead to increased diversion of methadone to the streets.

The study committee contacted and received reports from medical practitioners who have been licensed to use methadone to treat drug addicts; from the treatment agencies where methadone is regularly used; from drug free treatment programs; and from social workers and counsellors in the field of correction treatment and rehabilitation who are in daily contact with addiction problems. There appear to be four main reasons in Canada for the decrease in the total number of narcotic addicts being treated with methadone.

1. Changed attitudes on the part of physicians and concomitant loss of interest in methadone on the part of addicts.

It would appear that at least some physicians who once used methadone have become disillusioned with obtained results. In addition, there seems to be evidence that addicts, in general, are disenchanted. Reasons for this include the fact that oral methadone is not perceived by many addicts as an adequate substitute for intravenous heroin. Addicts are aware that methadone is just as addictive as heroin, and indeed withdrawal from it may be more difficult and prolonged. Many complain of the side effects of methadone such as constipation and loss of sexual drive. Addicts also seem to be worried about the dangers of methadone overdose.

2. Addict dissatisfaction with conditions imposed by some clinics.

The examples here include inflexibility in handling patients, and some degree of insensitivity to their daily needs. Addicts will not put up long with what they term a daily "hassle" in dealing with clinics. The necessity for daily visits to obtain methadone restricts their activities such as going away for a weekend. This is despite the fact that the lifestyle of the average junkie has long necessitated a daily contact with a pusher on the street, including the weekend days.

3. Changing trends in drug use.

This seems to be an important factor in Canada. There is a trend towards multiple drug use, and this is lessening the number of hard core addicts to opiates. Better enforcement activities by the police have reduced supplies of heroin, and at the same time have produced a lower grade of heroin available for sale. Individuals using this are not as heavily addicted as far as physical dependence is concerned. Most addicts use drugs such as tranquilizers, barbiturates, and alcohol to help them over periods of heroin non-availability. Lastly, there seems to be little doubt that a rapid increase in the use of cocaine is a factor in the decrease in heroin addiction. While some addicts use both heroin and cocaine the cost militates against heavy use; this again lessens the degree of physical dependency.

4. There is a tendency in Canada for programs to orient addicts towards a drug free state as a preferred future.

For this reason many clinics are moving to slow detoxification with methadone, rather than maintenance with it. There is generally more interest in drug free programs.

I have chosen to present this overview of arrests, deaths, drug seizures, of details of Canadian programs and success/failure rates. I trust that it has been of use as an introduction to this conference on continuation of international approaches to the prevention and treatment of the unfortunate victims of chemical dependence.

Thank you.

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Cultural Aspects of Alcohol and Drug Problems in Canada

Juan Carlos Negrete

This analysis of cultural trends in drug and alcohol abuse in Canada is based on a comparison with the U.S.A. and on differences observed between separate regions of the country. The subject is approached from an epidemiological standpoint in the hope that speculation on cultural influences would result from the study of quantitative evidence rather than from subjective impressions. This approach is, of course, not without its shortcomings and serious limitations: national statistics are scarce and tend to cover mostly items whose nature is perhaps too general to accurately reflect cultural variance. In addition, the comparability to data from separate countries or regions is frequently rendered difficult by differences in sources of information and in the methods utilized to gather them.

In comparing the sociocultural basis of drug and alcohol use in Canada and the United States, it is warranted to begin by adopting the null hypothesis, not simply as a matter of standard scientific procedure, but also because one can truly expect to find no major differences in cultural phenomena occurring in two societies which have so much in common. There are few countries in the world as much in contact with one another, sharing lifestyles to the same extent. Both populations are exposed to common mass media messages; they tune in to the same television stations on a daily basis. Canadians are frequently more aware of what is current in the United States than in other parts of Canada. The same consumer products are marketed simultaneously in both countries, often using identical commercial advertising. The mobility of persons across the border is practically unrestrained. These factors greatly facilitate cultural transmission and contribute to the development of similar habits and social attitudes in both countries.

In spite of these similarities and of the many historical, socioeconomic and political ties which unite these two societies, there are certain divergences which may be expected to differentially influence patterns of alcohol and drug use in them. An

important one is the ethnic and subcultural breakdown of their populations. The 1981 census data just released on the population of Canada (1) shows that the largest group (61.3 percent) is that of persons indicating English as their mother tongue. As in the United States, this group is composed mainly of the original British settlers plus descendants of earlier immigrant groups (Irish, German, Dutch, Scandinavian) who have been largely assimilated by them. But it also includes second and third generation descendants of other immigrant groups such as Italians, Greeks, Asians and Eastern Europeans who, on being questioned, would declare English as their mother tongue. The French-speaking group is the second largest (25.7 percent); with the exception of some very recent and as yet not significant additions (Haitians, North Africans), French mother tongue persons represent the original French Canadians.

Notable differences with the American population are, in the first place, this very large French minority. People of French origin in the United States represent 1.5 percent of the total population. Secondly, the important southern European minorities - Italians, Portuguese, and Greeks - in Ontario and Quebec (6 percent and 3.1 percent, respectively), and the Ukrainians in the Prairies (4.0 percent). Thirdly, the existence in the United States of two major ethnic groups not yet significant in Canada: blacks and Hispanics (11 percent and eight percent, respectively). This difference is important in relation to the problems of drug abuse, as these two groups appear to be particularly vulnerable.

Another important feature is the regional distribution of ethnic groups in Canadian society. A solid French majority in Quebec (82.4 percent) has created a veritable separation of cultures which appears to influence some aspects of the alcohol and drug abuse problem. There are in Canada some 370,000 natives who account for 1.5 percent of the total population. In the United States, on the other hand, a total of 800,000 native Americans represents less than 0.5 percent. Although in both countries natives tend to concentrate in certain regions, their numbers in the Canadian Prairies (5 percent) and the Northern Territories (34.5 percent) are a major influence in the regional picture of alcohol abuse.

Canadians are rather proud of the fact that different ethnic groups tend to keep their own traditions and retain their separate identities. This cultural trait makes Canadian society somewhat different from the American one where the homogenization of lifestyle is encouraged.

ALCOHOL USE

National per capita consumption figures demonstrate that Canada's pattern is closer to that of the United States than to

the ones in other related countries. Canada and the United States present medium overall levels which have increased at a similar pace over the years. (Table 1)

The similarity extends to beverage class preferences: both Canadians and Americans are heavy beer and light wine drinkers, a tendency observed in Britain and Australia as well. However, unlike those two culturally related societies, the consumption of spirits is much higher in North America. The picture in France is so markedly different, with 70 percent of the total alcohol intake in the form of wine, that French influence on Canadian drinking patterns may be considered as minimal. (Table 2)

The regional variance within Canada shows the highest total consumption levels in the Yukon and Northwest Territories. There is also a clear trend towards higher consumption in the western provinces: Alberta and British Columbia yield figures well above the national average. The higher overall levels in the West and the Northern Territories are accounted for almost entirely by high rates of spirits drinking; beer and wine figures appear to follow this asymmetric regional distribution. British Columbians drink the highest average amounts of wine in the country; this finding not only reflects the existence of a local wine industry, but also a tendency among west coast Canadians to follow closely social habits prevailing on the American west coast. As British Columbia, California presents the highest level of wine drinking in the country. The highest per capita total consumption levels in the United States are also found in the Pacific region.

Quebec shows the second highest figure for wine use in Canada, but it must be noted that sales statistics do not include homemade products. It has been well established that the majority of Italians, Portuguese and Spanish living in Montreal produce their own wine each year in amounts frequently beyond the allowed quota of 200 gallons per household (2). Since these ethnic groups constitute a sizeable minority in the province, consumption figures could be significantly influenced by this omission. (Figure 1)

The regional tendencies identified through beverage sales figures are supported by findings of general population self-report surveys on drinking. There are more drinkers in the western provinces and, more importantly, a considerably higher percentage of heavy drinkers. The tendency is particularly clear for females: the percentage of heavy drinking women in British Columbia and the Prairies is three times that in Quebec and the Atlantic provinces. One clear difference in alcohol use practices between Canada and the United States is the number of abstainers in the population of drinking age: 33 of 100 Amer-

icans as opposed to 25 percent of Canadians fall in this category. The percentage of heavy drinkers, however, is remarkably similar in both countries; an average of 6 surveys conducted in the United States during the period 1971-1976 indicates that 18 percent of males and 4 percent of females consume 14 or more drinks per week (3). (Table 3)

ALCOHOL-RELATED MORTALITY

Mortality due to cirrhosis of the liver is clearly higher in the U.S. than in Canada, both for males and females. Yet Canadian rates are closer to American ones than to those in the United Kingdom or France. Also, the male-female ratio of 2:1 is roughly the same in both countries, whereas it is considerably lower in Britain and slightly higher in France.

Regional liver cirrhosis mortality figures within Canada do not appear to correlate with local per capita consumption levels, as could be expected. Quebec, for instance, with much lower average consumption than Alberta, Ontario and Prince Edward Island, presents a higher rate than those provinces. Factors such as beverage class preference - beer vs. spirits - and alcohol use patterns - daily drinking vs. intermittent bouts - may be more responsible for differences in cirrhosis rates than the varying consumption levels. On the other hand, the regional variance in male-female ratios of alcohol-related deaths (alcoholism, alcoholic psychosis, liver cirrhosis, alcohol poisoning and suicide) does follow closely that of consumption patterns: it is 1:1 in the Yukon, while in New Brunswick and Quebec, where the percentages of heavy-drinking women are the lowest, the relation is 4 males for each female (4).

ALCOHOL-RELATED SOCIAL PROBLEMS

There are very few quantitative indicators of social behaviour which are suitable for cross-cultural comparisons. However, some alcohol-related social problems can be tallied and rates may be calculated. These indicators are more related to acute alcohol intoxication than chronic alcohol abuse and tend to depict alcohol-related public disorder rather than disturbances which occur in private. (Table 4)

The number of DWI offences in a given year varies widely across the different regions of Canada. The average rate for Canada is slightly higher than that for the United States, with the western provinces and the northern territories showing highly significant increases. It has been established that these areas present larger consumption volumes as well, but there are some environmental factors which may also contribute to the regional disparity in rates. For example, drinkers are more likely to be on the roads in sparsely populated rural areas where they must

travel some distance to and from public drinking places. This factor is particularly important where local attitudes do not favour drinking at home. An additional influence may be a cultural preference for distilled beverages and a pattern of heavy weekend intoxication. This is no doubt the case in the prairies, the northern territories and Prince Edward Island. (Table 5)

Rates for aggressive behaviour incidents also vary across different provinces. The number of violent crimes recorded by the police tends to follow the same direction observed with alcohol traffic offences, and the highest figures are found in the western region of the country. Admittedly, this type of offence is not as reliable an indicator of alcohol abuse as DWI reports, but the major role played by alcohol intoxication in violent behaviour cannot be ignored. Disorderly and aggressive behaviour under the influence of alcohol is one of the features of alcoholism more strongly linked to sociocultural factors and some of these could explain the regional variance in Canada. Jellinek, for instance, reported crosscultural differences in the social behaviour of heavy drinkers. He noted that in countries such as Switzerland, France, Italy and Portugal, middle-aged individuals were observed who appeared with physical complications of chronic alcohol abuse, such as cirrhosis of the liver, without having been identified as alcoholics earlier in their lives (5). They would apparently neither seek treatment nor be perceived as needing assistance for this problem in their milieu. The fact that their chronic abuse could go unremarked for so many years may reflect a high degree of cultural tolerance for heavy alcohol consumption, but it also shows that these heavy drinkers do not behave in a way that would precipitate an earlier intervention. These examples are societies where the prevailing pattern is one of regular daily use, mostly at home, and where alcohol is not philosophically perceived as evil.

Alcoholic behaviour tends to be more disturbed in those communities whose value systems include strongly critical views on drinking (6). A possible sociodynamic mechanism is that of the self-fulfilling prophecy. Individuals whose social milieu strongly cautions against the disinhibitory effects of alcohol are likely to act up the apprehended behaviour when intoxicated. They may, in fact, tend to drink with the purpose of releasing repressed impulses. A classic study by Skolnick on the social consequences of drinking experiences among American students found that those individuals belonging to religious groups with the strongest temperance views were the ones who became involved in more incidents after drinking (7). Prohibition was introduced mostly in countries where stronger puritanical religious beliefs prevailed. In Canada, a law was enacted which permitted each local government to impose prohibition in accordance with the results of a local plebiscite. The only province never to

introduce it is Quebec which, coincidentally, shows the lowest DWI rate and the second lowest violent crime figures.

Another factor that may account for the variance in rates of reported crime is differential police action. That is, police could be more inclined to intervene or to report in one region than in another. There are, unfortunately, no elements which could satisfactorily clear this question. However, it may be relevant to look at data gathered some years ago in a comparative study of alcoholics in treatment at a Montreal facility. These were all local residents and consequently subject to control by the same police force. (Table 6)

Even after allowing for age and years of drinking, alcoholics of Anglo-Protestant cultural identity were significantly more likely than French Catholics to be arrested for public drunkenness offences. Other parameters, such as permanence of marriage, also indicate that the former faced a higher degree of social difficulties and rejection. These findings are supported by those of a recent study by Babor et al. (8) who found French-Canadian alcoholics in the United States to show the second lowest rate of public drunkenness and disorderly conduct arrests among seven subcultural groups surveyed. The uneven distribution of these cultural groups in Canada may be a factor in regional rates of alcohol-related behavioural problems.

Differential police action, however, may be a real factor in the higher rates of alcohol offences registered in the Northwest Territories, the Yukon and the prairies, where the proportion of native population is the largest. In Canada, as in the United States, Indians and Inuit are particularly vulnerable to alcohol abuse problems; society at large, as well as its law enforcing agents, have come to expect natives to exhibit disorderly behaviour under the effects of alcohol. A vicious circle situation may have been created as natives tend to fulfill the prophecy. In British Columbia, for example, natives make up less than 2 percent of the general population but constitute 30 percent of jail inmates. The white-native ratio of referrals to psychiatric centres in that province, however, is 10:1. This evidence would suggest that behaviour problems normally handled by health services in the case of non-natives, tend to be processed through the justice system when presented by natives. Studies of patient populations in Alberta and Saskatchewan found that natives receive the "personality disorder" diagnosis significantly more often than non-natives. It was also observed that Indian and Metis patients were more likely than non-natives to have entered hospitals on an involuntary basis. Rates of admission for alcoholism are also higher among natives but this difference is accounted for by the number of females entering hospitals with that diagnosis since the percentage of male natives so labelled is actually lower than that of non-natives. It

would appear that there is a tendency to refer native female alcohol abusers to hospitals and male ones to jail (9) (10) (11).

In the United States, natives are twenty times more likely than whites to be arrested for public drunkenness and the ratio for violent crime convictions is 3:1; but these problems are not evenly distributed across the different sectors of the native population. French and Hornbuckle (12) have identified three separate sociocultural categories among them with respect to drinking behaviour: a) the traditional native Americans, representing no more than 20 percent of the total aboriginal population, and living isolated from mainstream culture, among whom alcohol intoxication is one within a set of ritual practices and appears to cause less social damage; b) the middle class natives, also called "white Indians," a selected minority representing the establishment-supported native spokespersons. They are in active Indian affairs bodies. Their pattern of drinking differs little from that of the non-native society; c) the marginal native Americans who form the largest group, accounting for some 65 percent of the total native population. They are neither traditional nor totally acculturated and display the highest rates of alcohol-related social problems.

In Canada there is an equivalent of these distinctions; the marginal natives are represented mostly by the Metis and the non-status Indians, also called non-treaty Indians. As the denominations indicate, these are people whose identity is most conflictive, finding themselves at a crosspoint between native and non-native cultures. They cannot fully identify themselves with either and have insufficient elements for developing their own. Surveys in Alberta and Saskatchewan have demonstrated that the Metis when compared with treaty Indians and Eskimo are the group with the highest rates of alcohol pathology (10).

PROBLEMS OF DRUG ABUSE IN CANADA

The United States has developed a multivariate monitoring system which has no equivalent in Canada. The DAWN and CODAP programmes, and the periodic national surveys, for example, have not yet been introduced in this country. An important exception is the province of Ontario where the Addiction Research Foundation has been systematically recording general population drug use trends since 1977. Currently available national drug use data originates mainly from two sources: one is the Federal Bureau of Dangerous Drugs which receives police reports of arrests and pharmacy thefts, compiles conviction statistics and keeps methadone treatment and "known user" files; the other is the federal police force (R.C.M.P.) which has information on crime reports, arrests and charges, drug exhibits submitted for analysis, street drug purity control tests, street drug availability and cost; and keeps a file on narcotic users.

The evidence thus collected points to some marked differences in the drug abuse pictures of Canada and the United States. The use of heroin, for instance, although a major drug problem south of the border, would appear comparatively insignificant in Canada, with the exception of the province of British Columbia where reside close to 70 percent of all known opiate users in the country. Vancouver is the port of entry for traffic coming from the Orient and it has the largest concentration of Asian immigrants who maintain active contact with Hong Kong and Indochina; consequently, greater availability of the drug in that city is a likely explanation for this regional disparity. It is also possible that many heroin users from other regions have gone to British Columbia following the closure of drug maintenance treatment programs in their home provinces. Methadone clinics which operated during the 60's in Montreal, for example, were discontinued a few years later, mostly due to little support from the public and the health profession community. An attitude of disapproval towards drug maintenance appears to prevail elsewhere in the country as well. In places where methadone is still used, it is given mostly within the context of shortterm detoxification protocols. It would appear that cultural support for continuing drug supply programs is more readily accorded in the United States than in Canada. The absence of high risk ethnic ghettos in the latter, and a relatively small number of addicts, markedly reduces the degree of local concern about this problem. The use of cocaine, on the other hand, seems to be equally prevalent in both countries; in Canada it is concentrated mostly within the larger urban centres (Montreal, Toronto, Vancouver).

Leaving tobacco aside, cannabis is the psychoactive agent most widely used for non-medical purposes across the country. Surveys conducted by Health and Welfare Canada in 1980 show that levels of use for respondents aged 18 years or younger are higher in Ontario and the western provinces than in the east. However, samples of adults yield a remarkably stable rate of 10 percent in all regions (13). When compared with the surveys conducted by Johnston et al. (14) in the United States, it would appear that the Cannabis-using population in Canada is smaller by a factor of 10 to 20 percent. Contrary to what climatic conditions might suggest, cannabis is also available in Canada through local production; the largest cultivation is concentrated in British Columbia where cannabis patches hidden in remote public forest are constantly being detected by the police through helicopter surveys. This illegal supply is reported to have increased considerably since the recent introduction of the sinsemilla variety, a high yield, shorter plant more difficult to detect from the air (15). (Table 7)

Findings from a 1981 survey of high school students in Ontario demonstrate the extent of prescription drug abuse in Canada. In

this sample, ranging in age from 13 to 18 years, the use of pharmaceutical psychotropics is particularly prevalent among the younger ones, and has grown since 1977 when a similar population was surveyed. The use of alcohol and cannabis, on the other hand, appears to have peaked in 1979 and shows a declining tendency in 1981. The latter finding correlates with cannabis use trends in the United States, but the abuse of psychotropic medications is definitely a greater problem in Canada. (Table 8)

This assumption is further supported by data from client populations in the United States and Quebec. There are marked differences in the primary drugs of abuse reported by individuals seeking help at publicly funded treatment centres in both locations. Whereas, in the United States, heroin abuse is by far the most prevalent problem; in Quebec, the largest percentage corresponds to the sedatives/hypnotics group of substances. It is difficult to speculate on "cultural" reasons for these divergences. A relevant factor may be the different degree of access to medical care in these two societies: Canadian health insurance programs allow for unrestricted contact with medical practitioners, and prescription drugs are likely to be more often reported; American drug rehabilitation centres are geared towards narcotics addicts - perceived as the major local problem - and have tended to neglect the care of other substance abusers.

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TABLE 1

APPARENT PER CAPITA CONSUMPTION OF ALCOHOLIC BEVERAGES IN LITERS OF ABSOLUTE ALCOHOL IN PERSONS 15 YEARS AND OVER

	YEAR	SPIRITS	WINE	BEER	TOTAL
FRANCE	1972	3.2	16.2	3.9	23.4
AUSTRALIA	1972-73	1.8	1.8	9.6	13.2
CANADA	1974	4.0	1.2	6.0	11.3
U.S.A. *	1975	4.5	1.3	5.2	11.1
U.K.	1974	2.1	1.1	7.7	11.0

* 14 YEARS AND OVER

Source: ADAPTED FROM MARK KELLER AND CAROL GURIOLI, STATISTICS ON CONSUMPTION OF ALCOHOL AND ON ALCOHOLISM. NEW BRUNSWICK, N.J., RUTGERS CENTER OF ALCOHOL STUDIES, 1976 ED. Reprinted by permission from Journal of Studies on Alcohol, Inc.

TABLE 2

PER CAPITA CONSUMPTION (LITERS ETHANOL) BEER, SPIRITS AND WINE. CANADA AND PROVINCES. TOTAL POPULATION. 1979.

REGION	BEER	SPIRITS	WINE	TOTAL
NEWFOUNDLAND	6.20	3.92	0.51	10.63
PRINCE EDWARD ISLAND	5.16	5.08	0.79	11.03
NOVA SCOTIA	4.89	4.44	0.97	10.30
NEW BRUNSWICK	5.05	3.44	0.73	9.22
QUEBEC	6.05	2.80	1.77	10.62
ONTARIO	5.61	4.44	1.51	11.56
MANITOBA	4.50	5.08	1.21	10.79
SASKATCHEWAN	4.70	4.56	0.85	10.11
ALBERTA	4.95	6.28	1.71	12.94
BRITISH COLUMBIA	4.65	5.88	2.44	12.97
NORTHWEST TERRITORIES	5.53	7.20	1.38	14.11
YUKON	8.61	9.72	2.77	21.10
CANADA	5.45	4.32	1.60	11.37

Source: STATISTICS CANADA, CONTROL AND SALES OF ALCOHOLIC BEVERAGES IN CANADA. CATALOGUE 63-202, 1979

TABLE 3

MORTALITY FROM CIRRHOSIS OF THE LIVER, RATE PER 100,000 POPULATION, 1974

	TOTAL	MALES	FEMALES
AUSTRALIA	8.3	11.6	4.9
CANADA	11.6	16.0	7.3
FRANCE	32.8	47.6	18.6
ENGLAND & WALES	3.6	3.8	3.4
SCOTLAND	6.3	7.2	5.4
U.S.A.	15.8	21.4	10.6

Source: W.H.O. (1977) Wld Hlth Stat Ann 1

TABLE 4

DRIVING WHILE IMPAIRED, OFFENCES REPORTED BY POLICE, BY PROVINCE, RATES PER 100,000 PERSONS, 1977

NEWFOUNDLAND	650.1
PRINCE EDWARD ISLAND	674.9
NOVA SCOTIA	490.6
NEW BRUNSWICK	500.2
QUEBEC	433.8
ONTARIO	511.1
MANITOBA	728.4
SASKATCHEWAN	906.9
ALBERTA	997.7
BRITISH COLUMBIA	900.9
YUKON	2,018.6
NORTHWEST TERRITORIES	1,794.4
CANADA	604.2

Source: STATISTICS CANADA. CRIME AND TRAFFIC ENFORCEMENT STATISTICS, CATALOGUE 85-205, 1977

TABLE 5

VIOLENT OFFENCE RATES PER 100,000 PERSONS, 1978

NEWFOUNDLAND	458.6
PRINCE EDWARD ISLAND	344.2
NOVA SCOTIA	523.1
NEW BRUNSWICK	433.6
QUEBEC	400.9
ONTARIO	621.1
MANITOBA	567.4
SASKATCHEWAN	593.1
ALBERTA	778.4
BRITISH COLUMBIA	871.0

Source: STATISTICS CANADA. CRIME AND TRAFFIC ENFORCEMENT STATISTICS, CATALOGUE 85-205, 1978

TABLE 6

PERCENTAGE OF SUBJECTS EXPERIENCING SOCIAL DIFFICULTIES, BY CULTURAL IDENTITY

	PUBLIC DRUNKENNESS ARRESTS	MARITAL BREAKDOWN	EARLY UNEMPLOYMENT	LIVING ALONE
F.C.	17	50	14	51
A.P.	48	85	44	80

Source: NEGRETE, J.C., CULTURAL INFLUENCES ON SOCIAL PERFORMANCE OF CHRONIC ALCOHOLICS. QUART. J. STUD. ALC. 34: 905-916, 1973. Reprinted by permission from copyright holder, Journal of Studies on Alcohol, Inc., New Brunswick, NJ 08903.

TABLE 7

DRUG USE* AMONG HIGH SCHOOL STUDENTS,ONTARIO, 1981

DRUG	PERCENT
TOBACCO	30.3
ALCOHOL	75.3
CANNABIS	29.9
STIMULANTS	21.2
BARBITURATES	20.6
HALLUCINOGENS	14.9
SEDATIVES	12.4
GLUE & SOLVENTS	5.5
COCAINE	4.8
HEROIN	1.5

*
AT LEAST ONCE IN PRIOR 12 MONTHS.

ADAPTED FROM SMART ET AL., ADDICTION RESEARCH FOUNDATION, TORONTO, 1981

TABLE 8

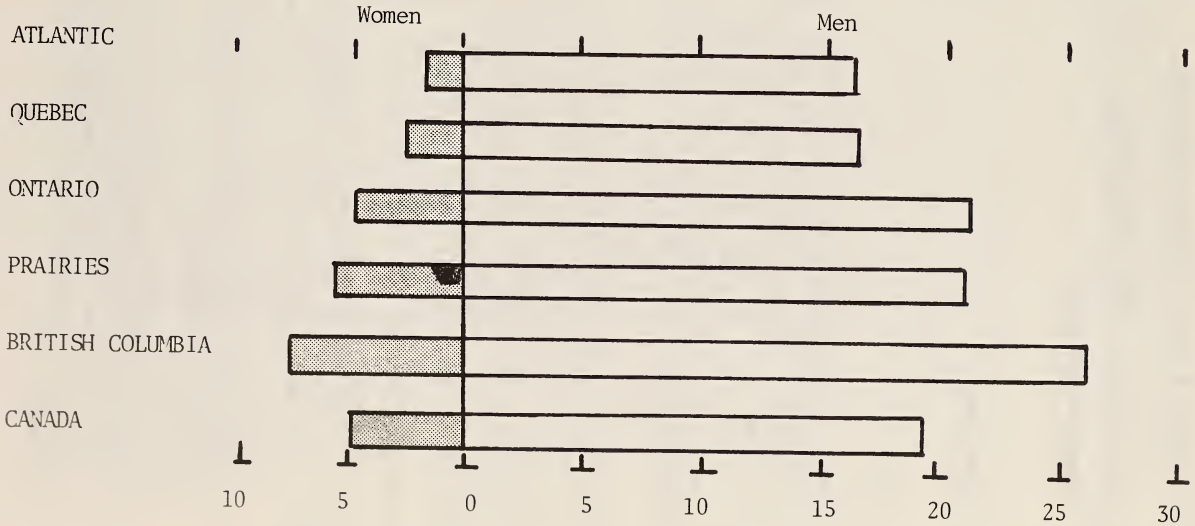
PERCENT DISTRIBUTION CLIENTS, 1978

PRIMARY DRUG	U.S.A.	QUEBEC
HEROIN	51.7	8.0
SYNTHETIC NARCOTICS	6.7	4.6
MARIJUANA	13.5	14.5
AMPHETAMINES	6.0	10.6
BARBITURATES	4.6	8.0
ALCOHOL	9.2	12.4
COCAINE	2.7	9.0
HALLUCINOGENS	5.2	13.0
SEDATIVES/HYPNOTICS	4.8	16.6
INHALANTS	1.5	3.3

Sources: CODAP DATA, U.S.A.
ALTERNATIVES, QUE.

FIGURE 1

* PERCENTAGE OF HEAVY DRINKERS BY SEX AND REGION, 1978-79



* CONSUMERS OF 14 OR MORE DRINKS PER WEEK

SOURCE: CANADA HEALTH SURVEY, STATISTICS CANADA CATALOGUE 82-538E

The Addiction Research Foundation—Mandate, Role, and Directions

Joan A. Marshman

INTRODUCTION

Mr. Chairman, I am delighted that the Committee on Problems of Drug Dependence elected to hold its 44th Annual Scientific Meeting in Toronto. Not only does this venue ensure an opportunity for those of us in the Addiction Research Foundation (A.R.F.) to "show off" our city while exchanging views with our international colleagues, but it represents the salvation of our travel budget which is currently reeling from the widening gap between the Canadian and U.S. dollars.

I see my task for today as sharing with you the "flavour" of the Addiction Research Foundation in the context of the Canadian approach to problems of drug dependence. My perspective will be managerial rather than scientific in character, and I will attempt to shed some light on the Foundation's mandate and organization, its program areas and goals areas, and its approaches to future effort.

MANDATE AND ORGANIZATION

The Addiction Research Foundation was established by the Government of Ontario in 1949. This initiative of the Provincial Government reflected several factors, among them:

- the constitutional responsibility of the Provinces (rather than of the Federal Government) to provide health care services;

- the Provincial Government's decision to permit the opening of Ontario's first cocktail lounges, and the vocal negative response from several sectors of the community, including the Temperance movement and the churches; and

- the efforts of H. David Archibald, who was actively involved in the mental health field, both provincially and nationally, and became the Foundation's first Executive Director.

This Foundation, established by Provincial statute, with responsibility for research directed to a single type of health problem, and reporting annually to the Legislature via the Minister of Health, constituted a model in the Province for the subsequently established research foundations in the areas of cancer and mental health.

The initial legislation gave the Foundation responsibility in the area of alcoholism. Not until 1961-62 was the mandate broadened to include "drug addiction," and the name changed to the Alcoholism and Drug Addiction Research Foundation. By statute the mandate of the Foundation has three dimensions: research, treatment, and information dissemination (which is more commonly referred to, internally, as "education"). It is noteworthy that the Foundation's responsibilities for information dissemination include specifically the dimension of "prevention," and in this respect this Foundation is unique among the Province's statutory foundations.

The initial research efforts were effected through a program of extramural grants to university scientists, but more recently the program has been focussed intramurally and is located largely in Toronto. Although the Foundation's treatment services were established initially in Toronto, its outpatient services (along with education services) were subsequently diffused to many Ontario cities. However, in 1969, the Foundation, with the Minister of Health's agreement, clarified and focussed its role with respect to treatment. Specifically, it undertook to concentrate its treatment efforts within the framework of treatment research, demonstration treatment models, and education and training for health and social service personnel, rather than in widespread direct treatment service delivery; thus, the Foundation currently provides treatment services only in its headquarters building in Toronto.

Today the Foundation has a total (1982-83) budget of $26.4 million and a full time staff of 694, located in its Toronto headquarters and in offices in Ontario cities. Administratively it is organized into six Divisions: the Clinical Institute, Social and Biological Studies, Education Resources, School for Addiction Studies, Regional Programs, and Administration and Support Services. In terms of the mandated responsibilities, the allocation of functions to these Divisions is indicated in Figure 1 (on the following page).

Figure 1

Divisional Allocation of the Foundation's Mandated Responsibilities

Research	Social and Biological Studies Division Clinical Institute Division Regional Research Centre (Regional Programs Division)
Treatment	Clinical Institute Division Regional Programs Division
Information Dissemination	Education Resources Division School for Addiction Studies Clinical Institute Division Regional Programs Division

THE FOUNDATION'S PROGRAM AREAS AND GOALS

Perhaps a more useful perspective on the Foundation's programming is that developed along the functional lines identified in Figure 2. As indicated in the Figure, these program areas are not discrete and isolated; rather, the current management thrust is directed to ensuring that they are appropriately interactive.

Some of the implications of such an interactive approach to programming are clear, for example:

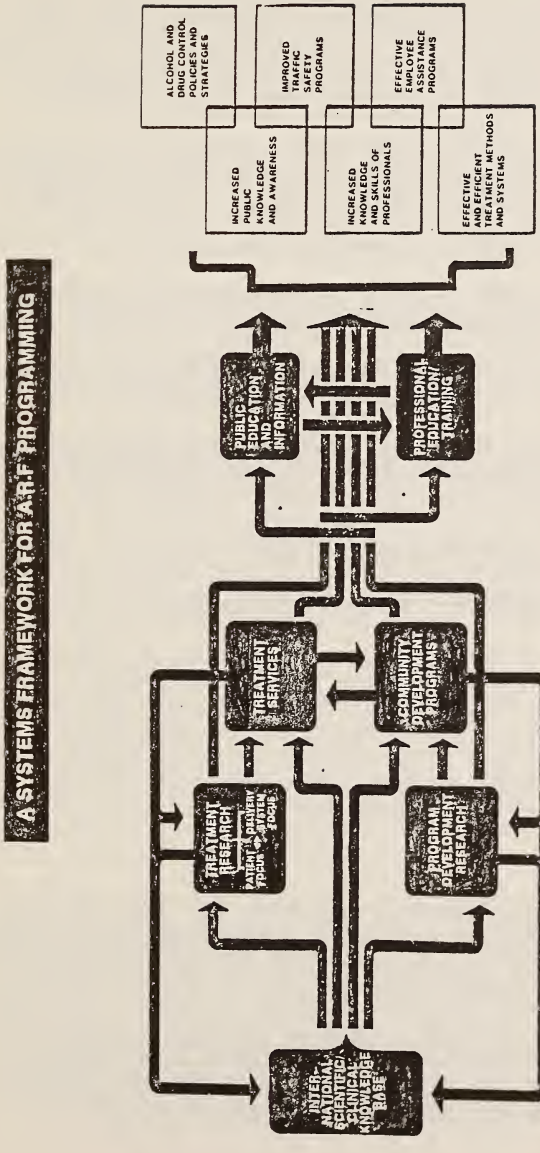
- a "building" process from research to education (including policy advice), so that the Foundation's information, training, and advice has largely a research base, rather than a moralistic or legal base; this tends to alienate some other organizations whose "causes" the Foundation cannot support;

- a need for not only information dissemination to the community but also feedback loops from the community-based staff to the research programs; and

- the opportunity and challenge to the Foundation of effectively mobilizing its information so as to "sell" its efforts to the community and government as being relevent and cost-effective, on the basis of their impact on prevention, treatment services, and policy advice.

Other consequences of this interactive system may be less readily apparent, and include:

Figure 2


A SYSTEMS FRAMEWORK FOR A.R.F. PROGRAMMING
INTER-NATIONAL SCIENTIFIC KNOWLEDGE AND KNOWLEDGE BASE
TREATMENT RESEARCH
PATIENT & DELIVERY SYSTEM FOCUS
PROGRAM DEVELOPMENT RESEARCH
TREATMENT SERVICES
COMMUNITY DEVELOPMENT PROGRAMS
PUBLIC EDUCATION INFORMATION
PROFESSIONAL EDUCATION/ TRAINING
INCREASED PUBLIC KNOWLEDGE AND AWARENESS
INCREASED KNOWLEDGE AND SKILLS OF PROFESSIONALS
EFFECTIVE ARF EFFICIENT TREATMENT METHODS AND SYSTEMS
ALCOHOL AND DRUG CONTROL POLICIES AND STRATEGIES
IMPROVED TRAFFIC SAFETY PROGRAMS
EFFECTIVE EMPLOYEE ASSISTANCE PROGRAMS

- the need to nurture effective dialogue between research staff and community-based staff, and particularly the need to ensure that the implications of research findings for community programs are effectively communicated; and

- the fact that the Foundation's position or advice on any question is continuously subject to change over time as a function of new information, with the result that the Foundation is periodically subject to some criticism about the inconsistency of its position.

But to what ends are these program efforts directed? The goals of the Foundation have recently been reviewed and reformulated, and the goal areas are identified in Figure 2. They include:

- increased public knowledge and awareness;

- alcohol and drug control policies and strategies which take into account public health aims;

- increased (addictions-related) knowledge and skills of (health and social service) professionals;

- effective and efficient treatment methods and systems (for individuals with alcohol- and drug-related problems);

- improved traffic safety programs;

- effective employee assistance programs.

This representation of the goal areas clearly has a "community impact" flavour, consistent with the interactive system described above which suggests that "the job is not done until the Foundation's work has had an impact on the community." However, the detailed goal statements are actually formulated in a manner which emphasizes the research base for the efforts which will be directed to achieving the goals.

FOUNDATION DIRECTIONS

Any attempt to enumerate research directions for the future is fraught with risk. Therefore, it seems more appropriate to share with you a sense of the factors which bear on the Foundation's decisions concerning research priorities.

Traditionally, Foundation priorities have been determined by assessment of "need," which might be defined hypothetically by both the frequency of the problematic alcohol or drug use in this Province and this Country and the severity of its

consequences. (In this context assessment of consequences must take into account not only the risk of morbidity and mortality for the individual user, but also the costs to the community in lost productivity, family and social problems, and law enforcement costs.) On this basis, research into alcoholism and tobacco dependence are seen by the Foundation as having higher priority than research focussing on opiate/opioid dependence. (Clearly this is an oversimplification, for it ignores the potential of narcotic research to illuminate mechanisms which represent common pathways or models for other drugs; however, while such research is, in fact, carried on within the Foundation, it has a somewhat lower overall priority.)

Coupled with "need" there must, of course, be opportunity -- a knowledge base adequate to permit identification of productive "next steps" which have a high probability of contributing to the appropriate types of human and material resources.

In the context of this approach to priority setting, the area of benzodiazepine research has been particularly problematic. Certainly this class of drugs is widely used in Ontario, but assessment of the benefits versus risks associated with their use has been a complex task.

Finally, with respect to research, resource limitations require careful decision-making with respect to the balance of basic vs. pre-clinical vs. clinical studies. This has been a serious consideration for the Foundation in the area of cannabis research, for which long term clinical studies would seem to have particular importance; at present the Foundation is not engaged in such research, at least partially because of the demand that such studies would place on its available resources.

In the case of treatment services the Foundation's priorities are two-fold: to provide a treatment system and treatment programs in its Clinical Institute Division in Toronto which, in addition to serving as the locus of treatment research efforts, and of some professional training programs, represent models for the community; and, through community development efforts, to promote and facilitate the development of appropriate treatment services in all areas of the Province.

The Foundation's gradual withdrawal from Province-wide direct delivery of treatment services, beginning in 1969, was not complemented by the systematic integration of alcohol and drug treatment services into the existing health care system, as had been envisaged. Instead, treatment services development has been quite uneven across the Province. However, within the last decade the Ministry of Health has established District Health Councils (D.H.C.'s) throughout the province as local advisory bodies to coordinate the development of appropriate health

services in each district; some 26 D.H.C.'s have now been established and the Foundation's Regional Programs Division staff is actively involved with 19 of these D.H.C.'s working towards the development of a rational plan for treatment services delivery to individuals with alcohol and drug problems, in the context of the general health and social services systems.

Consistent with the Ministry of Health's position on health care services delivery, the Foundation is advising:

- a community-based system of alcohol and drug treatment services which will optimally involve existing health care and social services resources;

- the establishment of patient assessment and primary care capacities as integral parts of the system;

- an emphasis on outpatient treatment services, with access to living accommodation where specifically justified on the basis of assessment findings, rather than a view that inpatient treatment facilities represent the cornerstone of the system.

Further, through programs directed to business, industry and labour, the Foundation is providing consultative services for development of employee assistance programs.

It is important to remember, however, that the Foundation neither funds nor operates the treatment services system in the Province, with the result that its achievements in this area are a function of its proselytizing for its proposals, and its function as a catalyst or facilitator within communities.

The Foundation's professional education and training programs reside in two Divisions -- the Clinical Institute (a teaching hospital of the University of Toronto) and the School for Addiction Studies. To date, the programs of the School for Addiction Studies have been directed primarily to training of A.R.F. staff. However, the top priority for the forseeable future rests in treatment-related training of health care and social services staff from community agencies. Clearly this direction is complementary to the thrust towards a community-based system of treatment services.

Finally the Foundation has recently formulated a plan for its public education activities for the '80's which is characterized by:

- an emphasis on alcohol, tobacco, and cannabis;

- a focus on pre-adolescents, adolescents and young adults (together with persons who influence young people, including teachers and parents);

- a focus on opinion-makers, gatekeepers, and influencers in professional and other community groups;

- efforts directed to the mass media, to provide maximum access to relevant scientific data available from the Foundation (rather than the development of large paid media campaigns).

As a government agency established in a Province which has been governed by a single political party for more than 30 years, A.R.F. has not been subject to the type of political turbulence experienced by alcohol and drug programs in some other jurisdictions. However, as the Government of Ontario has sought to reduce its deficits and to achieve a balanced budget, the Foundation has experienced some significant erosion of its grant, over the past 5 or 6 years. Further, as the Province faces the prospect of decreased federal transfers to health care, it is giving increased attention to the cost effectiveness of all of its health efforts. Clearly "accountability" is today's password!

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Recent Advances in Opiate Detoxification: Clonidine and Lofexidine

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INTRODUCTION

Recent studies (Gold et al.1978; Washton et al.1980) showing that the nonopiate antihypertensive agent, clonidine hydrochloride, suppresses signs and symptoms of opiate withdrawal have suggested that clonidine and similar drugs might be useful in the clinical management of opiate detoxification. The fact that clonidine is not an opiate drug and does not itself produce addiction or euphoria suggests some unique and potentially useful applications of this medication in the treatment of opiate-dependent persons. For example, clonidine might be used to block the emergence of abstinence symptoms during a gradual methadone detoxification. Clonidine might also serve as a transitional treatment between opiate dependence and induction onto the long-acting opiate antagonist, naltrexone (Resnick et al.1979). If withdrawal symptoms were controlled by clonidine, patients might be able to abruptly discontinue chronic opiate use and remain abstinent during the minimum 10-day opiate-free period that is required before starting naltrexone aftercare treatment. In general, clonidine might increase the chances of detoxification success and allow patients greater access to naltrexone and drug-free modalities.

Since the initial reports of clonidine's withdrawal-suppressing effects in opiate addicts, a variety of clinical studies have explored the usefulness of this medication in opiate detoxification, as reviewed recently by Washton and Resnick (1981). The present paper will summarize the outpatient studies conducted at New York Medical College with patients addicted to heroin and/or methadone. It will also describe our recent studies of lofexidine, an analogue of clonidine that appears to be a safer and more effective nonopiate treatment for opiate withdrawal.

CLONIDINE

Our first study (Washton et al. 1980) sought to replicate the single-dose findings of Gold et al. (1978) in order to gather additional information on the physiological and subjective effects of clonidine

in opiate-dependent humans. A single oral dose of 0.2 or 0.3 mg clonidine was administered to 12 opiate-dependent outpatients experiencing acute withdrawal from heroin and/or methadone. Blood pressure and ratings for the presence and severity of withdrawal symptoms were taken immediately before clonidine administration and at 2 hours postclonidine. The data showed that clonidine produced a marked and significant reduction in subjective withdrawal severity. The particular symptoms reduced most effectively by clonidine were chills, lacrimation, rhinorrhea, yawning, stomach cramps, sweating, and muscle and joint aches. Marked reductions in anxiety and restlessness were also reported. Side effects were dry mouth, drowsiness, and a decrease of 10-15 mm Hg in systolic and diastolic blood pressure. None of the 12 subjects experienced euphoria or any other opiate-like effects from clonidine, and none reported unpleasant side effects.

We subsequently explored clonidine's usefulness as an adjunct to methadone dose reductions and also as a transitional treatment during the 10-day period between opiate dependence and naltrexone. In an initial outpatient trial (Washton and Resnick 1980a) with 20 methadone-dependent volunteers, an attempt was made to determine whether clonidine could be used to prevent emergence of abstinence symptoms during the course of gradual methadone dose reductions. This study addressed the issue of prophylactic blockade of the abstinence syndrome in contrast to the previous studies that used clonidine to reduce ongoing withdrawal symptoms. Patients taking 10-50 mg methadone daily were inducted onto clonidine doses of 0.5-0.9 mg per day before initiating methadone dose reductions of 5 or 10 mg per week. All patients had been taking clonidine for at least 2 weeks before the methadone detoxification was begun. Ten of the 20 patients (50 percent) reached a zero methadone dose and remained opiate-free on clonidine for 10 days before starting naltrexone. Although the patients who successfully completed the detoxification generally complained of less severe and fewer symptoms than the patients who failed, it was evident that clonidine did not totally prevent the emergence of withdrawal symptoms. Patients who complained of intense withdrawal discomfort tended to be those who had been taking clonidine for more than 3 weeks, suggesting the development of tolerance to clonidine's antiwithdrawal effects.

In another outpatient trial (Washton et al. 1980) clonidine was administered to 88 opiate-dependent volunteers following abrupt discontinuation of methadone or heroin. Forty-three patients had received methadone 5-40 mg daily (mean 15 mg), and the other 45 patients had been taking illicit methadone or heroin in varying doses. On day 1, all patients received placebo methadone and started a self-administered clonidine dose regimen of 0.1 mg qid with gradual increases as needed over succeeding days. The maximum daily clonidine dose averaged 0.8 mg (range 0.3-1.2 mg). On day 10, patients who showed opiate-free urines and denied using any illicit opiates while on clonidine were given a naloxone challenge of 2.0 mg IV to assess their readiness to begin treatment with naltrexone. Seventy-two percent of the 43 methadone maintenance patients and

50 percent of illicit opiate users completed detoxification and started naltrexone treatment. Those who were on the higher doses of heroin and/or methadone had the greatest difficulty in completing detoxification. All patients reported that clonidine reduced, but did not eliminate, their withdrawal discomfort. Lethargy and insomnia were the most frequent and persistent residual complaints. Most patients experienced some mild dizziness or lightheadedness upon standing, but these side effects were unacceptably severe in only six cases. No single clonidine dose regimen was best for all patients, because sensitivity to clonidine's effects varied widely among individuals. To achieve effective control of withdrawal symptoms without untoward side effects, it was necessary to individualize the clonidine dose regimen according to each patient's blood pressure and symptomatology.

Rawson et al. (1981) provided additional evidence of clonidine's effectiveness in outpatient opiate withdrawal and found that the availability of naltrexone aftercare treatment significantly increased detoxification success rates. Among patients offered clonidine as a transitional treatment between methadone and naltrexone, 9 of 12 (75 percent) achieved 10 days of opiate abstinence and started naltrexone, whereas only 3 of 12 (25 percent) in a group offered clonidine but no naltrexone achieved 10 days abstinence. The differential efficacy of the clonidine detoxification procedure between the two groups of subjects did not appear to result from differences in the degree to symptom relief, but rather from different subject attitudes toward their detoxification. Subjects in the clonidine/naltrexone group perceived the clonidine detoxification as a transitional treatment with a specific goal. Naltrexone induction on day 10 postmethadone was perceived as a clear endpoint to the detoxification. Subjects in this group frequently expressed the feeling that they had "made it" when they started naltrexone and many reported feeling relief that once on naltrexone they no longer had to struggle with the urges and cravings to use opiates. It appeared that if the clonidine procedure was perceived by subjects as being for a specific number of days with a clear goal and endpoint such as starting naltrexone, most of them could exert sufficient control to abstain from opiate use for the 10 days of postmethadone. Subjects in the clonidine-only group did not view the detoxification process as having a clear endpoint or goal and this seemed to contribute to their inability to resist opiate cravings.

Although the clinical studies summarized above were encouraging, none compared clonidine against other detoxification methods. We recently reported a double-blind outpatient study (Washton and Resnick 1980b) in which 26 volunteers dependent on methadone (15-30 mg daily) were randomly assigned to a clonidine or methadone detoxification procedure. The clonidine procedure (N=13) consisted of abrupt substitution of clonidine for methadone on day 1 of the study. The methadone procedure (N=13) consisted of methadone dose reductions of 1 mg per day until a zero dose was reached. Both procedures were placebo controlled with daily regimens of active or placebo clonidine tablets individualized by a physician who was not aware of the patient's assigned treatment group. No significant difference

was found between the clonidine and methadone procedures in terms of the numbers of patients who completed a 10-day opiate-abstinence period after the last dose of active methadone. Four of 13 subjects (38 percent) were successful with clonidine, and 6 of 13 (46 percent) were successful with methadone ($P < 0.05$, chi-square test). Major withdrawal symptoms were nearly identical for both groups and consisted mainly of lethargy, restlessness, and insomnia. The clinical course of subjects was distinctly different for the clonidine and methadone procedures, making it impossible to maintain truly double-blind conditions. Subjects taking clonidine reported sedation, dry mouth, occasional dizziness, and onset of withdrawal symptoms within the first 2-3 days of the study. By contrast, subjects taking methadone reported no sedation, dry mouth, or dizziness, and no major withdrawal symptoms until the final week of the procedure when methadone doses were approaching zero milligrams.

LOFEXIDINE

Clonidine's efficacy in suppressing opiate withdrawal has suggested that other alpha-2 noradrenergic agonists might also be effective in opiate withdrawal but without untoward side effects. Lofexidine is an investigational analogue of clonidine that has been shown to suppress opiate withdrawal in morphine-dependent rats (Shearman et al. 1980). Clinical testing in human hypertensive patients (Wilkin et al. 1981) has suggested that lofexidine's sedative and hypotensive effects are less potent than those of clonidine.

We have recently completed an open clinical trial of lofexidine in opiate detoxification (Washton et al. 1981). As in our earlier studies with clonidine, the clinical test of lofexidine's usefulness was conducted in an outpatient setting with the measure of detoxification success defined by induction onto naltrexone. Our subjects were 15 methadone-dependent male outpatient volunteers who showed no evidence of medical or psychiatric illness and gave informed consent to the study which involved an abrupt switch from methadone to lofexidine. On day 1, subjects received their usual methadone dose (10-25 mg) and began a self-administered lofexidine dose regimen of 0.1 mg two or three times daily. On day 2, methadone was abruptly discontinued with subjects receiving a matched placebo methadone solution and the lofexidine dosage was increased to 0.1 mg four times daily. Subsequently, the lofexidine dose was increased as needed to no more than 0.4 mg four times daily according to symptoms and side effects. All subjects were told that the detoxification procedure would take 11 days and that naltrexone could be started on day 11 (10 days postmethadone) provided that they used no illicit opiates during the study as confirmed by the absence of a precipitated withdrawal reaction to intravenous naloxone challenge (2.0 mg) on day 11. Subjects who did use illicit opiates during the first 10 days postmethadone were allowed to continue on lofexidine and the naloxone challenge was postponed to the first opportunity where it posed minimal risk of precipitating a withdrawal reaction (i.e., to at least 5 days after the last opiate use) but no later than day 21 of the study. Subjects who passed

the naloxone challenge and started naltrexone on days 11-21 were considered successful detoxifications. Those who returned to using opiates and failed to begin naltrexone by day 21 were considered unsuccessful.

Successful detoxification and induction onto naltrexone was accomplished with 10 of the 15 subjects. All patients rated lofexidine as moderately to extremely effective in reducing most of the commonly experienced withdrawal symptoms: insomnia, lethargy, and muscle/bone pain were the most frequent residual complaints. None of the 10 subjects reported unacceptable withdrawal symptoms while taking lofexidine. Those who failed to complete the detoxification procedure cited opiate craving rather than withdrawal discomfort as the major reason for returning to opiate use. None of the subjects reported oversedation, dizziness, or lightheadedness from lofexidine, despite rapid increases in the dose to as much as 1.6 mg per day within the first 5 days. The maximum daily lofexidine dose ranged from 0.6 mg to 1.6 mg across the 10 subjects with an average of 1.2 mg. There was no significant lowering of blood pressure even at the maximum lofexidine dose (mean prelofexidine BP; 115/74 mm Hg: mean BP at maximum lofexidine dose; 115/76 mm Hg). Dry mouth and mild drowsiness were the most commonly reported side effects. Reductions in the daily lofexidine dose by 0.2 to 0.6 mg per day at the end of the study produced no symptomatic complaints or significant changes in blood pressure.

DISCUSSION

While our studies of clonidine suggest the usefulness of this nonopiate agent in outpatient opiate detoxification, it has also become clear that clonidine is not without clinical risks and potential drawbacks and thus is not an ideal agent for treating withdrawal symptoms. Some patients are extremely sensitive to clonidine's hypotensive and sedative effects and cannot tolerate the doses needed to relieve withdrawal discomfort. This has led patients to discontinue their detoxification before completion and has seriously restricted the usefulness of clonidine in outpatient withdrawal to patients whose level of opiate dependence is below 30 mg/day of methadone. Additionally, the close monitoring of patients that is required because of potentially troublesome side effects during clonidine treatment can be inordinately time-consuming and inconvenient for both patient and physician. These factors tend to decrease the efficacy and acceptability of clonidine detoxification especially in an outpatient setting where side effects can interfere with the patient's daily functioning.

Our results with lofexidine suggest that this medication is comparable to clonidine in terms of antiwithdrawal efficacy but without the adverse sedative and hypotensive side effects that limit clonidine's usefulness. It appears, therefore, that lofexidine might be a more clinically useful and viable treatment than clonidine in opiate detoxification, especially with ambulatory outpatients where safety and ability to maintain normal functioning are important concerns. Additionally, because lofexidine can be administered

in higher doses than clonidine without unacceptable side effects, it might be possible to detoxify outpatients from higher levels of opiate dependence than has been the case with clonidine.

Nonopiate treatment with clonidine or lofexidine may be specifically indicated and preferable to detoxification using methadone in some cases. For example, these agents may be the treatment of choice for addicts with low levels of opiate dependence whose addiction might be increased by the use of methadone. Clonidine or lofexidine may be especially useful in treating iatrogenic addiction to prescription opiates and treating addicted physicians or others having no prior involvement with illicit opiates where exposure to methadone or methadone treatment facilities might be undesirable or contraindicated. In general, clonidine and lofexidine may provide potentially useful and desirable treatment options whenever detoxification using methadone is inappropriate, unsuccessful, or simply unavailable.

Clonidine and lofexidine seem best suited for clinical use as transitional treatments between opiate dependence and naltrexone. Nonopiate medications with significant withdrawal-suppressing effects can provide symptomatic relief following rapid discontinuation of opiates without postponing the introduction of naltrexone at the earliest possible time to foster continued abstinence. The treatment sequence of clonidine or lofexidine followed as soon as possible by naltrexone induction is highly attractive to outpatients because it offers the opportunity for rapid detoxification with minimal discomfort and a clearly defined endpoint to the detoxification process.

The role of detoxification treatment alone as a therapeutic modality has long been overemphasized in addiction treatment. Attempts to detoxify large numbers of opiate addicts using clonidine or lofexidine, based on expectations that these patients will remain abstinent without some form of intensive aftercare treatment, are highly unrealistic. In most cases, readdiction will rapidly ensue. Addicts are extremely vulnerable to relapse, particularly during the first week or two following cessation of opiate use. Although clonidine and lofexidine might be extremely useful in helping addicts achieve initial abstinence, a more comprehensive multi-modality aftercare treatment approach including naltrexone and psychotherapy is usually necessary in enabling detoxified addicts to maintain an abstinent state (Resnick et al. 1981).

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Methadone Maintenance: An Update

Edward C. Senay

It is only in the last two decades that we have acquired an extensive experience with the use of legal opioids in the treatment of opioid dependence. While our experience is modern the concept of providing legal opioids to the opioid dependent is distinctly not modern. In history the earliest mention of such a concept appears to be in Siam in the 1850's when the King of Siam decreed that the state would give opium to persons addicted to opium. The first direct American experience with the concept of narcotic substitution was at the turn of the century when we took over the Philippines and inherited a state-administered narcotic distribution system.

For a time we utilized morphine for maintenance in some of our major cities but in the 1920's court interpretations ended our brief experience with this notion. In the 1950's a joint committee of the New York State Medical Society and the American Bar Association called for exploration of the concept and, as everyone in this room knows, Drs. Dole and Nyswander carried out a series of studies on the potential of methadone. These studies formed the base for an enormous expansion of this treatment in America in the last two decades. In the brief time available, I want to comment on our experience with methadone treatment.

Drs. Dole and Nyswander reported on the success of their experiments in the middle 1960's and some one hundred and fifteen studies later one can say that their findings have held up, perhaps not to the same degree of initial success because their studies quite rightly excluded the more complicated cases which had to be treated when the method gained approval for widespread use.

To say that their findings have held up is not a casual statement. Methadone maintenance has been evaluated more than any other human service modality with the possible exception of psychotherapy. The public is not aware that this is the case, and there is virtually no public recognition that the evaluations of

methadone maintenance are almost uniformly favorable. Surprisingly, many workers in the field of substance abuse share with the public lack of awareness of the extent of the outcome research which has been carried out on methadone and many also appear to be unaware of the favorable findings of this research.

It is important to stress that the studies which have been carried out have encompassed years of observation, thousands of patients, and that independent groups have been involved. The General Accounting Office of Congress (GAO), for example, reviewed the reviews of the effectiveness of methadone maintenance and reported to the U.S. Congress that it was an effective treatment modality. But, persistently, a common critique of the outcome research on methadone maintenance repeats what Dr. William Martin said at the Second National Methadone Conference in 1969 to the effect that we don't have double-blind studies which would permit us to evaluate this modality scientifically. This critique is no longer valid because we do have one double-blind study with random assignment reported in the Lancet in 1979. Newman and Whitehead recruited 100 heroin addicts in Hong Kong for a double-blind study which lasted for 36 weeks. The study actually was biased against the hypothesis that methadone is superior to placebo because both groups received methadone in the induction phase of the study. The experimental group was maintained for the 36 weeks of the study while the control group was withdrawn from the daily induction dose of 60 mg. of methadone during the first 60 days. This study was, in effect, a study of methadone maintenance versus methadone detoxification. Large differences were observed between experimental and control groups, the differences being favorable for methadone maintenance.

In the face of data accumulation almost unparalleled in history, complete with one double-blind study with satisfactory methodology, the message that methadone works hasn't gotten through. How can we account for the public and, in large measure, those who work in the field being unaware of or unaffected by the data? Part of the reason stems, no doubt, from the factionalism so prominent in the field of substance abuse. For example, workers in the alcohol treatment community tend to be biased against the basic concept of legal substitution. "It's like giving an alcoholic bourbon". The Therapeutic Community groups have long been hostile to the notion of substitute therapy and a host of workers, unfamiliar with the clinical realities of opioid dependence, find the substitution concept difficult.

Part of the reason also appears to be the cautious way in which evaluators worded their findings. If one reviews the evaluations, one does not find simple statements to the effect that the data indicates that the treatment works. Why evaluators have been so hesitant is a matter of conjecture; a good guess is that the turbulence and politicalization of the field gave them pause.

Some may be ambivalent about methadone substitution because we have not carried out replicated, and I underline replicated, double-

blind studies of the effectiveness of maintenance treatment. Given the current climate of anti-intellectualism and public suspicion of research it is doubtful that further double-blind studies can be carried out. In the event that they are, let us hope that we institute control for factors such as degree of dependence. We have many studies now indicating that applicants for methadone treatment vary from no dependence on opioids to severe dependence on opioids. Studies by Blachly, Resnick, Goldstein, O'Brien and Senay indicate that this is the case. Improving diagnosis along the lines suggested by Dr. Sellers' work at the Addiction Research Foundation here in Toronto is urgently needed. If we could measure psychological dependence it would be desirable to control for level of psychological dependence occurring at any given level of biologic dependence. Control for these factors would delineate more precisely what methadone contributes.

Recent work by the Philadelphia group suggests that psychiatric status is another factor which contributes substantially to variance. The most serious methodologic obstacle in studying legal maintenance relates to the fact that we are studying a problem that tends to take the form of a career, lasting at least ten and, frequently, many more years. Obviously, we need to design studies which cover long periods of time.

Another factor possibly explaining the discrepancy between data and awareness is the large impact of a few poorly administered programs; the bad press associated with these programs has impeded progress in recognizing the usefulness of methadone and has in some communities, in Oklahoma and California for example, led to abandonment of this modality.

The verdict of clinicians is almost uniformly favorable; that is, those most in touch with the day-to-day realities of treatment of opioid dependence with methadone are impressed with what it has to offer. Part of the problem with public recognition of this treatment stems from the fact that only a relative handful of professionals have experience with methadone maintenance and until recently their interest had little visibility in so-called "main stream medicine" and no visibility in the public sector. Since their interests were and are professional, they simply didn't write for the public. Those writing for the public tended to be journalists whose tenure in the field tended to be brief. I'm thinking of people like Edward Jay Epstein whose exposure to the field was at most one to two years. Epstein wrote a review of methadone and damned it for its purportedly evil political utilization. His article, in the journal Public Interest, was widely read and had an impact on the attitudes of important people in government. The Public Interest refused to print my letter reviewing the many errors of omission and commission in the Epstein paper. So we haven't done a good job with public relations.

A recent NIDA Treatment Research Report presents evaluation results from therapeutic community as well as methadone maintenance and drug free treatment. We, who work in the field, need to

review and to know these data. For too many years people who work in substance abuse have been either blind proponents of one modality or apologetic about what we do. If the people in the field won't read the outcome studies they should not be surprised that the public has attitudes based on a lack of awareness of the data. Again, I would call your attention to the number of subjects involved in these studies. It is in the tens of thousands. Although the study does not display Sells latest writing, the time periods included in these most recent outcome studies are now close to two to three years and the results remain favorable.

A causal relationship between treatment and the favorable outcomes observed is, in my opinion, is not definitively established by these studies either individually or in the aggregate; maturation, regression toward the mean, reduction of symptoms following the crises in which patients usually seek treatment, lack of replication, random assignment and lack of adequate control groups, the use of remaining samples and other problems with methodology mean that we can only say that treatment is associated with desirable outcomes and probably produces the results we see. The NIDA monograph from which these slides were made does not mention other large scale studies of outcome such as those published by Newman et al. in New York, Goldstein et al. in Palo Alto and Senay et al. in Chicago. These three reports document additional thousands of patients studied for extended periods of time and in concert with the studies mentioned in the NIDA monograph demonstrate that desirable changes are associated with treatment.

In passing one should also note that, although this is less true now than it was in 1970, methadone maintenance is a treatment which is attractive to consumers. Over the past decade and one half, addicts numbering in the 100,000's have utilized this treatment. This is no small point. Ideally one would wish that all these addicts could have been persuaded to accept treatment with narcotic blocking agents such as cyclazocine or naltrexone. But the fact is that the consumers of addiction services will not accept such treatment in numbers which are significant from a public health point of view.

Length of stay in maintenance has declined sharply in the past decade. In 1970 more than one half stayed in treatment over a year but in 1980 the figure was close to 25%. I believe that there are at least three factors involved in the change of consumer attitudes. One, the most powerful in its impact, is the change in the nature of our drug problems; to illustrate, in 1968, in Illinois, 80% of those seeking maintenance treatment used heroin as a sole drug or the main drug of abuse. That is, these patients used heroin with occasional use of another drug such as marijuana or alcohol. In 1978, in Chicago, this figure was down to 18%. So the consumer has changing needs. The second factor relates to our poor public relations record. Again many, perhaps most, of the workers in the field have ambivalent attitudes at best toward opioid substitution therapy. Another factor was the impact of regulation on progress. The adversarial approach used by regulatory agencies

in the United States helped to worsen the natural divisions among workers in the field and generated the kind of low morale which was reflected in Dr. Dole's paper on the subject in the Journal of the American Medical Association.

With the sharp reduction in resources experienced in the last few years, the question of long term goals of maintenance has assumed renewed importance. Currently we see administrators asking if we can't get successful patients on chronic maintenance detoxified so we can use their slots to treat new patients. But our collective experience is not encouraging in this regard. Withdrawal from legitimate narcotics is as problem-ridden as withdrawal from illicit narcotics, and the logic of exchanging a proven success for an uncertain success is shaky. Ideally one would wish for a drug free state but for many thousands of addicts that is, as yet, an unreachable goal. Some can reach this goal and we should continue to try, but we know the odds are against successful detoxification of successful chronic methadone maintenance patients.

The safety of chronic administration of methadone under medical auspices is impressive. In some instances, patients have been taking daily methadone for a decade or more and are suffering no medical consequences. Indeed the clinical impression one has is that the health of addicts improves dramatically when addicts use the treatment to stop intravenous drug use. Hepatitis, endocarditis, systemic infection and soft tissue infections certainly seem to be greatly diminished during chronic methadone, as would be predicted from cessation of the use of unsterile needles.

A number of recent large-scale studies suggest that treatment for drug and alcohol problems greatly reduces further utilization of the standard medical care system in the years following substance abuse treatment. Roughly speaking, a dollar spent on treatment for substance abuse appears to prevent two to three dollars of future expenditures on visits to hospitals and outpatient offices and clinics. In Illinois, a current study is under way attempting to document further this relationship. Again workers in our field ought to know and should be able to acquaint legislators and community leaders with the relevant data.

The dilemma of the pregnant active opioid addict seems to have been at least partially solved by the utilization of low dose methadone maintenance throughout the pregnancy and delivery. Prior to the past decade clinicians attempted to withdraw pregnant addicts and did not realize that the human fetus frequently will die in narcotic withdrawal. This is in contrast to the adult addict who dies so rarely in narcotic withdrawal that there is real question if some complicating factor must not be present to produce death. Early attempts at high dose maintenance of the mother were associated with severe post-natal problems for the neonates. Finally, low dose maintenance evolved and appears to be the best solution to a difficult problem. Use of any opioid, licit or illicit, may be associated with an increase in the occurrence of

the Sudden Infant Death Syndrome (S.I.D.S.). The data, at this time, is suggestive but not conclusive of such a relationship. The attribution of causality is usually not possible because of the use of multiple substances by most opioid-dependent pregnant women.

When the decade started there was serious doubt by many that there was an association between heroin dependence and crime. There was also little data concerning the effects, if any, of treatment on criminal behavior. The data base bearing on this question has grown enormously. The preponderance of evidence now strongly supports the notion that active phases of heroin dependence are associated with a substantial increase in the crime rate and that treatment, including but not limited to methadone maintenance, is associated with a substantial reduction in the rate of commission of crime. The relationship appears to hold in different ethnic groups in the United States. On this ground alone Drs. Dole and Nyswander deserve our highest awards.

The question of high-dose versus low-dose maintenance was raised by a number of studies in the early seventies with the general conclusion that retention rates and outcome in treatment were as favorable at low doses as they were at high doses. I don't regard the issue of dose as closed, however, because of my belief that the opioid-dependent population of 1982 is bi-modal with respect to degree of dependence. In my opinion, there are large numbers of addicts probably not needing strong opioid agonists such as methadone. It is time that we carried out maintenance studies comparing weak with strong opioid agonists under double-blind conditions.

The question of staffing of methadone maintenance programs is still not settled. Although the para-professional, or community worker, has succeeded in contributing to progress by creating for the consumer a sense of familiarity, commonality of language and custom and a role model, the training of such counselors has not provided them with the skills they need to compete with standard professional groups. Licensure and certification for this group of workers, however distasteful, is necessary for their survival.

It is surprising that, in 1982, we have no substantial body of data which would permit us to judge what contributions various staff members make, if any. For some patients the mere provision of methadone appears to be clinically potent while for other patients, many other patients in my view, the provision of methadone alone has little or no payoff. We tried to study this in Illinois but resources did not permit us to study the matter properly. Obviously it is a matter, in these times of diminished funding, that we should examine in rigorous clinical studies. The idea that methadone would work by exposing people to treatment has not been resolved satisfactorily. We don't know why we get the results we get, and it is obviously something we need to examine critically in the future.

In putting this program together we agreed to review the recent advances in the particular area each of us was to review. In preparing this paper I asked myself repeatedly the question, What have been the advances in methadone maintenance over the past fifteen years? In thinking about these years, the events that came to memory most immediately and forcefully are those in which we reacted to attack from the media, from auditors, regulators, reviewers, inspectors, commissioners and interrogators in a line which would have given Kafka material for two or three more careers. There was threat of assult from ideologues of every persuasion ranging from the National Caucus of Labor Committees (members of this group threatened my life repeatedly) to the mindless libertarians who appear to want free access for all people, including children, to any and all psychoactive substances. The basis of the fundamental assault was that they viewed us not as physicians working in communities with few resources, with difficult clinical populations, often under dangerous conditions, but rather as adversaries, often viewed as members of the "Drug Abuse Industrial Complex" with the implication of a sybaritic, criminal lifestyle based on stealing from the government. NIDA, to its everlasting credit, did see to it that we were evaluated and the evaluations speak for themselves. So, although we've spent most of our energy on defense we have made one advance of great importance. We've shown that treatment is associated with desirable outcomes and the burden is now on those who say that it isn't.

We have not improved narcotic substitution therapy as we might have if we had lived in less troubled times. The failure to get LAAM through the bureaucracy is distressing. I regard LAAM as a form of methadone maintenance and know this drug in clinical settings. LAAM clinics especially in cities like Chicago where public transportation for our patients is expensive and extremely time consuming would represent a major advance which would permit us to improve our services and to focus more energy on new and/or difficult cases. I hope the CPDD will interest itself most vigorously in the LAAM matter.

At the beginning of the decade, I hoped that we would come to require licensing and certification for physicians working in methadone programs. Methadone prescribing for maintenance and detoxification is not within the competence of every physician. Substance abuse is a specialty — not a specialty with highly developed techniques like cardiac surgery or burn care but it is nonetheless a specialty. We have paid a high price by not recognizing this fact. We could improve the entire field by requiring training for physicians and all other workers before they work in methadone programs.

No review of narcotic substitution therapy would be complete without examining the effects of sponsorship; that is, who is administering the substitute narcotic and for what purpose. Drs. Newman and Dole cautioned us early in our national experience of the dangers of merging medical treatment with the criminal justice system. Their concerns were echoed by members of President Carter's

Commission on Mental Health who called our attention to the "insidious" possibilities in such a relationship. If a court orders treatment and the treatment of choice on the part of the patient and physician is methadone, has an "insidious" merger occurred? What is our experience in this regard? First we should note that in most of the major cities of America substantial numbers of applicants for any treatment of narcotic dependence have an active relationship with a criminal justice system. In my experience an "insidious" merger has not occurred. Treatment diversion programs have served well the individual, families and communities involved. Court decisions influenced by communication from workers in treatment programs like myself have been a near daily experience of mine for over a decade. This experience does not lead me to want to change the relationship or to fear that somehow, because in the abstract it could be bad, we should avoid the relationship. Given the crowded situation in the nation's jails and prisons I predict a large expansion of diversion programs in the 1980's and believe that it would be criminal not to include opioid substitution therapy as one of the possibilities for diversion.

In 1982, as never before, the multi-modality concept developed by Jaffe is most relevant. Methadone, for maximum public health effectiveness should be part of a treatment system and it should not stand alone. The continued use of alcohol and opioids is now the rule, not an exception. The changes in the nature of our substance abuse problem argue strongly for this position. Chicago, for example, has changed dramatically since 1967; the abuse of weak agonists such as pentazocine has come to occupy a large part of the sector of clinical demand. Methadone is, therefore, not as central as it once was in our clinical efforts. The drug experimentation and use patterns identified by Dr. Lloyd Johnston in the nation's high schools suggest strongly that we will need multi-modality programming for the foreseeable future. Dr. Johnston's data indicates that the use of multiple substances appears to be the dominant mode among those who will come to our attention in the future.

We have made some progress on the problem of detoxification from chronic methadone maintenance in that we have learned to go slower. In some instances, we can get patients drug free after some years of successful maintenance but these patients, as I noted above, are more of an exception than a rule. When this decade started, I had high hopes that we would find a path back to drug free living but this clinical dream has not been realized.

In summary, then, we have not changed clinical use of methadone significantly in the past decade but we have proven that its use is associated with desirable outcomes. I think that we know more now about what needs to be studied and we know that we have to improve training and staffing. Opioid substitution therapy has contributed substantially to public welfare and, in the future, we should be able to increase its contribution based on our experience of the last two decades.

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Psychotherapy for Opiate Addicts

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SUMMARY

An opportunity to receive a six-month course of professional psychotherapy in addition to paraprofessional counseling was offered to opiate addicts who were beginning a new treatment episode on a methadone maintenance program. The treatments offered were drug counseling alone (DC), counseling plus supportive-expressive psychotherapy (SE), or counseling plus cognitive-behavioral psychotherapy (CB). Sixty percent of patients meeting the study criteria expressed an interest in the psychotherapy program and 60% of these actually became engaged. One hundred and ten subjects completed the study intake procedure, were randomly assigned to one of the three treatment conditions and kept three or more appointments within the first six weeks of the project.

A variety of outcome measures showed that patients in all three treatment groups improved. Patients receiving the additional psychotherapies improved in more areas and to a greater degree than those who received counseling alone. The specific improvements seen appear to be related to the focus of the therapy used. Patients with antisocial personality disorder, as defined by Research Diagnostic Criteria, did not benefit significantly from therapy, but those with depression did. Patients with high levels of psychiatric symptoms made many significant gains if they received additional therapy, but improved only in drug use if they received counseling alone. Patients in all three treatment groups having low levels of psychiatric symptoms improved significantly in many areas.

We conclude that more than a third of opiate addicts in our treatment program are interested in psychotherapy and many of these can benefit from it. Certain administrative procedures appear necessary to maximize the chances that psychotherapy can be used effectively with drug addicted patients.

INTRODUCTION

There is some evidence to suggest that psychotherapy may be both practical and helpful with addicts if given under certain conditions. The development of methadone maintenance treatment programs has provided a means to reduce much of the intense, impulsive and daily search for illicit substances that is observed in private practice. Stabilization with methadone has permitted the development of therapeutic, long term relationships and thus, in theory at least, methadone programs might provide a medium in which psychotherapy could be employed effectively. In addition, the most recent study on psychopathology in methadone - maintained patients showed that depression and not sociopathy is the most commonly diagnosed psychiatric disorder, though sociopathy is certainly well represented (Rounsaville et al. 1982). Further, about half of those patients with a diagnosis of sociopathy also have other psychiatric problems. Thus, there is reason to believe that psychotherapy may be capable of providing benefits to addicts, especially if it is delivered in a methadone treatment program.

Background Work

No published studies on the effectiveness of psychotherapy with this population appear to have been done prior to 1970. The one exception was the early work of Nyswander et al. (1958) which was completed before the development of methadone treatment. The overall conclusion reached from a review of the few studies done is that there is evidence to indicate that psychotherapy can be helpful for opiate-dependent patients. This type of review and conclusion is similar to that reached by Luborsky et al. and others in their overviews of many diverse psychotherapy studies of treatment efficacy for psychiatric patients in general (Luborsky et al. 1975; Smith et al. 1980; Andrews and Harvey 1981). These reviews found that 65 percent of the patients in the psychotherapy outcome studies showed a treatment effect.

PRESENT WORK: THE PENN-VA PSYCHOTHERAPY STUDY

This paper reports the results of a controlled study done to test whether professional psychotherapy can provide additional benefits when combined with standard drug counseling services in a methadone treatment program. The study was done in the methadone treatment unit of the Philadelphia VA Medical Center. This treatment unit is one of eight methadone programs in the Philadelphia area and has an active census of about 350 patients. It is a full service program which is mandated to treat all veterans who apply. The program's administration has always conceived of drug dependence as being related to life

events such as social or psychiatric problems. Therefore, services provided include, where appropriate, drug and social work counseling, vocational rehabilitation, and medical consultation. Psychotropic medications are also used along with methadone and drug counseling to treat psychiatric problems that accompany the addiction.

Administrative Procedures

Prior to beginning the study we gave considerable thought to the administrative procedures that might be used in a psychotherapy program with this special population. We had completed a previous study of family therapy with addicts in 1976 and that experience was of considerable help because we learned that there are special conditions under which therapy has the best chance to work (Woody et al. 1981). Based on this experience we expected three problems to occur: 1) missed appointments by patients; 2) competition between counselors and therapists; and 3) loss of morale by therapists in response to the nature of the addicts' problems.

We implemented a series of procedures from the start of the study, in a largely successful attempt to combat these anticipated problems. These are described in detail elsewhere, as are the treatments used (Woody et al. 1983).

Subjects and Methods of Recruitment

Patients selected were all males, between 18 and 55 years of age, were nonpsychotic, did not have a persistent or clinically significant organic brain syndrome, and met FDA requirements for methadone maintenance treatment. They had been on methadone for at least two weeks but not more than six months during their current treatment episode and were screened to exclude those who appeared to have serious medical, legal, or personal problems that would require their moving from the Philadelphia area within one year.

Design - Patients were randomly assigned to three treatment conditions upon completing intake: Drug Counseling alone (DC), Supportive-Expressive psychotherapy plus counseling (SE), and Cognitive-Behavioral psychotherapy plus counseling (CB).

Patients who completed the intake procedure were required to keep three appointments with their counselor and therapist in the first six weeks (total of six appointments), or with their counselor if they were assigned to DC alone (total of three appointments). If they failed to keep these three appointments, they were considered nonengaged and dropped from the study. About 80 percent of the patients who completed intake kept these initial appointments.

Measures - A schedule of a sample of the measures used is given in table 1.

Another highly objective set of measures were the records of drugs used by patients during the six-month study period. The drugs of particular interest were methadone prescribed for maintenance treatment; ancillary psychotropic medicines prescribed for treatment of psychiatric symptoms; and urine test results for illicit drugs.

RESULTS

(1) Interest and Participation of Patients

It is a common opinion of both professionals and non-professionals that drug-addicted patients are not interested in psychotherapy. Our results show this is not so. Most patients who fit the intake criteria were asked if they wished to participate. Approximately 60 percent of the patients who were asked said they were interested in the project, and about 60 percent of these completed the intake procedure plus the three initial appointments. Patients who were interested appeared to be no different from those who declined. Some who declined appeared to do so out of practical considerations such as extended job hours. Thus, while participation was by no means universal, there was a substantial number of patients who demonstrated interest in the psychotherapy as an addition to their drug counseling.

(2) Benefits Achieved by the Patients

The data to be presented in this section represent the seven-month ASI evaluations, the psychological test results, and the methadone doses, ancillary psychotropic medications prescribed, and urine test results for opiates and other abused drugs. Specifically, data are presented for all patients in each group who completed their intake evaluation plus the initial three appointments. Composite scores and single items from the ASI as well as psychological test scores for each treatment group can be seen in table 2.

The clear overall result was that patients in all three groups improved in many outcome measures, including lessened drug use, crime days, illegal income, and improved psychological function.

The data also indicate that patients who received psychotherapy in addition to drug counseling made more and larger gains than those who received drug counseling alone. The SE group showed twelve significant changes; the CB group showed nine, and the DC group showed seven significant changes from intake to seven-

month follow-up. The SE patients' gains were especially prominent in the areas of psychiatric symptoms and employment. All patients improved significantly in the drug use factor, with DC and SE patients improving more than CB patients.

Some very significant group differences are also seen when one compares the medications used by patients in the three treatment groups. There are significant differences in the average methadone dose required for the three groups. The average dose for DC patients increased significantly ($p < .01$) up to week eight where it leveled off at about 43 mg/day, which is approximately the average dose used in the clinic. CB patients' doses also rose and leveled off but then gradually but significantly ($p < .01$) decreased. SE patients' doses were approximately level for about 15 weeks and then decreased. The mean methadone dose prescribed over the course of the study was significantly higher for the DC group than for the two therapy groups, which did not differ from each other.

It is important to mention that decisions for methadone dose changes were not made by the therapists. Patients usually initiated the discussion about the question of a medication change and the counselor formed an opinion. The situation was then presented to a clinic physician if the counselor felt that a change was necessary. The physician sometimes met with the counselor and patient and other times acted on the counselor's recommendation without seeing the patient. All these procedures are standard clinic practice and were not initiated simply for the study. Five physicians were working in the clinic during the study and only one of these physicians was a therapist. This physician saw eight therapy patients, and decisions about medication changes for his patients were made by one of the other M.D.'s.

The mean percentage of patients prescribed an ancillary psychotropic medication was significantly higher in the DC group ($F=52.31$, $p < .01$) than the psychotherapy groups which did not differ from each other ($p > .10$). Further, there was a significant increase in the proportion of DC subjects who were prescribed ancilliary medication ($p < .01$), while the two therapy groups showed significant decreases ($p < .01$) over the course of the study.

One to three urines were collected weekly for each patient on days that were chosen at random. All groups showed a significant decrease in positive urines over the course of the study ($F=8.41$, $p < .05$) but there were no differences among the three groups ($p > .10$). There was significantly more variability in the urine test results for the DC group than for either of the therapy groups. We also examined opiate - positive

urines separately from any other illicit substances. Again all three groups showed a significant decrease over the course of the study ($F=11.81$, $p<.01$). However, in this analysis the patients receiving the additional psychotherapy showed a significantly less use of opiates than the patients who received counseling alone ($F=$ $p<.05$).

The last analyses presented here were done to see if there were subgroups of patients who responded differentially to therapy or to counseling. These analyses are seen in table 3 which shows results of treatment outcome in therapy or counseling for patients in each treatment group with either high or low levels of psychiatric symptoms, as measured at study intake. The upper and lower thirds of the composite scores were used to produce this table, with the middle group (mid-severity patients) being excluded.

As seen, low-severity patients achieved many significant gains under each of the three treatment conditions. High-severity patients assigned to the additional therapy groups showed many significant improvements, but those high-severity patients who received only counseling showed progress only in reducing their drug use. These results suggest that the supplemental psychotherapies made a significant difference in outcome for the high severity patients and produced a level of improvement that did not occur if they received drug counseling alone.

Finally, we analyzed the data to see if psychiatric diagnosis was a predictor of outcome. To accomplish this end we looked at treatment outcome in patients who received therapy who had RDC diagnoses of opiate abuse only, those who had opiate abuse and depression, and those who had only opiate abuse and antisocial personality disorder. Both therapy groups were combined in this analysis in order to achieve a sufficient number of subjects in each category.

The largest therapy effect was observed in those patients with depression and there was no significant effect in patients with only antisocial personality disorder except that drug use was reduced. These findings are supportive of the idea that psychotherapy is not helpful for people with sociopathy. Preliminary analyses of outcome according to individual therapists or counselors show that there are significant differences in the treatment effect achieved by specific individuals. Several therapists produced much better results than others, and the same was true for counselors.

It is necessary to comment on a limitation in this project, which is the unbalanced design. Patients treated in the therapy groups saw a helping person (therapist or counselor), an average of 23 times whereas those in the DC alone group saw their counselors an average of 17 times. Thus, the patients in the therapy groups spent about 35 percent more time with a helping person than the DC alone patients. This design was deliberate since our aim was to see if the addition of professional therapy to counseling services would provide extra benefits. This question was the major practical issue addressed by the project. We never considered it reasonable that therapists could be used to replace counselors. However, we do think it is practical and advantageous for psychotherapy to supplement the important role of counselors with certain patients. We are also interested in the question of total time spent with a helping person vs outcome and have begun to study this issue.

We find it interesting to speculate about why the psychotherapy provided the ingredients necessary to permit a reduction in drug use without the necessity to elevate the methadone. One central factor in this regard was the development of a supportive relationship between the patient and the therapist. Some authors in the field have theorized that drug dependence is a substitute for certain aspects of important personal relationships (Fenichel 1945) such as in the case of an alcoholic who brings out three bottles of his favorite liquors and greets them as reliable old friends. Under this view it is possible that the personal therapeutic relationship formed in psychotherapy became a direct substitute for drug use. However, we think that the benefits of psychotherapy are more than simply the results of a relationship. Observations that we made during this study and in other therapy situations suggest that the benefits of therapy are a result of the therapists' ability to form a relationship combined with special knowledge and skill about how to use it. We have noticed that many of the counselors form good patient relationships but have trouble managing them, especially with the very disturbed patients. It should also be remembered that, like other patients who have been treated with psychotherapy, opiate addicts often have significant psychiatric problems, especially in the areas of depression and anxiety. To the extent that drug use is an attempt to medicate these problems and to the degree that psychotherapy can reduce them, psychotherapy can reduce drug use indirectly.

It is important to mention in closing that there are substantial predictors of the benefits received by adding

psychotherapy to counseling. These predictors are related to the severity of psychiatric symptoms and psychiatric diagnoses, especially depression and antisocial personality. These predictors and the effect of therapy plus counseling vs. counseling alone speak to potential areas where additional psychotherapy might be used to improve ongoing treatment services.

REFERENCES (Available upon request)

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TABLE 1

SAMPLE OF MEASURES USED

	INTAKE	1-MO	7-MO.	12-MO.
CONSENT FORM	X			
SCHEDULE FOR AFFECTIVE DISORDERS AND SCHIZOPHRENIA - LIFE TIME VERSION (SADS-L) (26)	X			
MAUDSLEY PERSONALITY INVENTORY (27)	X	X	X	X
BECK DEPRESSION INVENTORY (28)	X	X	X	X
SOCIAL ADJUSTMENT SCALE (29)	X	X	X	X
SCL-90 (30)	X	X	X	X
SHIPLEY (31)	X			
RELATIONSHIP INVENTORIES (32,33)		X		
SCHEDULE FOR AFFECTIVE DISORDERS - CHANGE VERSION (SADS-C) (26)	X	X	X	X
ADDICTION SEVERITY INDEX (ASI) (34)	X	X	X	X

TABLE 2

	SE 32 START		SE 32 7-MO.	CB 39 START		CB 39 7-MO.	DC 39 START		DC 39 7-MO.	7-MO. ANCOVA
EMPLOYMENT FACTOR	129	**	14	127	*	51	90		44	.01 SE* (CB,DC)
Days Worked	7	**	15	6		8	10		12	.01 CB* (SE,DC)
Money Earned	256	**	614	307		372	369		382	.001 SE* (CB,DC)
DRUG USE FACTOR	182	*	123	198	*	146	208	**	120	.05 CB* (SE,DC)
Days Opiates	6	**	2	8		5	7	**	2	.05 CB* (SE,DC)
Days Sedatives	4		2	3	.07	1	5		3	.01 DC* (SE,CB)
Days Stimulants	3		2	1		1	2		1	N.S.
LEGAL FACTOR	236	**	121	250	**	74	168	.08	78	.05 SE*CB*DC
Crime Days	7	*	2	7	**	1	5	*	2	.07 DC* (SE,CB)
Illegal Income	178	**	75	347	**	129	138	*	88	.10 CB* (SE,DC)
PSYCH FACTOR	203	**	116	184	*	156	183		159	.01 SE* (CB,DC)
Beck	15	**	8	14	*	10	13		10	.01 SE* (CB,DC)
Maudsley N	27	*	21	27		24	26		21	N.S.
SCL-90	187	**	139	178	*	127	166	*	142	.01 DC* (SE,CB)
SADS-Anx	19		18	19		18	18		19	N.S.

* = $p < .05$
** = $p < .01$

Range of appointments: 3-24

SE average - 12 sessions
CB average - 9.3 sessions
DC average - 17 sessions

TABLE 3

START TO SEVEN MONTH IMPROVEMENT

	LOW-SEV 12			HIGH-SEV 10			LOW-SEV 10			HIGH-SEV 11			LOW-SEV 12			HIGH-SEV 10		
	Start		7-MO.	Start		7-MO.	Start		7-MO	Start		7-MO.	Start		7-MO	Start		7-MO.
MEDICAL	164		211	158		208	186		168	286		309	203		211	326		348
Days Med. Prob.	4		8	4		6	4		2	9		11	5		5	13		16
EMPLOYMENT	138	*	13	90	+	18	132		107	136	+	42	68		27	98		106
Days Worked	5	*	17	10	+	14	6		8	6	+	10	10	+	16	10		9
Money Earned	138	*	746	308	+	500	231		214	243		321	348		399	270		285
DRUG USE	123		120	148	*	116	138	+	101	208	*	122	146	*	92	226	+	140
Days Opiates	2	+	0.4	5	*	1	4		4	5	*	1	6	*	1	6		4
Days Stim.	1		3	3		1	2		1	1		0	1		1	4		1
Days Dep.	3		2	4		5	4		0	7	+	3	1		2	11	+	4
LEGAL STATUS	148	*	66	168	+	101	107	+	51	231	+	101	98		52	116		103
Crime Days	4	+	1	5		2	3	*	0.4	8	+	2	2		2	3		2
Illegal Income	79	+	14	98	+	58	95	+	20	211	*	45	27	+	4	61		66
PSYCH STATUS	164	*	78	219	*	170	132	*	69	194	*	130	134		92	194		169
Psych Sev.	1.8	+	1.0	5.4	*	3.2	0.8		0.7	4.8	*	1.8	1.6		1.0	5.1		4.3
Beck	11	*	5	19	*	11	10	*	6	18	*	9	9	+	4	15		15
SCL-90	60	+	24	101	*	64	42	*	21	84	*	42	47	+	33	71		56
Maudsley N	23	*	12	35		31	15		13	32	+	24	21	+	17	38		33
SADS Tot.	44		39	57		52	46		42	59	+	46	47	+	43	58		62
GAS	75	+	86	55	*	72	66	+	75	54	+	70	71		74	58		64

* = $p < .01$
+ = $p < .05$

Opioid Antagonists: Do They Have a Role in Treatment Programs?

Charles P. O'Brien, Robert A. Greenstein, Bradley Evans, George E. Woody, and Robin Arndt

The rationale for using opioid antagonists is based on the provision of a nondependence-producing drug to protect the detoxified addict from readdiction despite his returning to areas of high drug availability.

This paper will concentrate on naltrexone and only briefly mention buprenorphine. We will not discuss the history of opioid antagonists although this is a fascinating story in itself. These drugs have helped to define concepts like physical dependence, and they have been instrumental in the discovery of opiate receptors and endogenous opiates. Drugs like nalorphine, naloxone and cyclazocine have been used for treating dependence clinically and discarded for various reasons over the past 15 years.

Naltrexone has been used in clinics since 1973. It is still an investigational drug and its prospects for approval for general use remain uncertain. Let us examine the important issues of safety and efficacy.

SAFETY

Animal toxicity data indicate that naltrexone has a wide margin of safety. LD 50's in several species are quite high and chronic administration studies also indicate lack of toxicity. Several years ago there were rumors in the treatment community that naltrexone may be carcinogenic. That notion was based on the misinterpretation of some interim data in a rat chronic toxicity model. In fact, a full range of testing has found naltrexone to be noncarcinogenic and one model even suggests some anti-tumor activity (Braude 1980).

Over 2,000 human subjects have been treated with naltrexone, most for a few weeks but some for as long as two years. Toxic effects have been few. The usual dose is 50 mg per day or 350 mg per week in two or three doses. However, up to 800 mg per day have been given without apparent toxicity (Verebey 1980). There have been several cases of skin rash and one case of idiopathic thrombocytopenic purpura which cleared on cessation of the drug and these may have represented immune reactions.

The most commonly reported naltrexone side-effect has been gastrointestinal distress. This usually occurs early in treatment, and in some cases, it may represent a mild precipitated opioid withdrawal reaction rather than a side-effect in the usual sense.

There are other naltrexone effects which relate to its pharmacological actions separate from blocking re-addiction to opioids. A wide spectrum of opioid receptors are affected by naltrexone and this can be expected to influence the role of these receptors in normal physiology. The hypothalamic-pituitary-gonadal axis is a good case in point. Mendelson and colleagues (Mendelson et al. 1979, Ellingboe et al. 1982) have reported that naltrexone produces a prompt rise in luteinizing hormone (LH) in both normals and recently detoxified addicts. Cicero and co-workers (1979) have reported similar findings in rodents leading to theories about the mechanisms of the pulsatile release of LH. Normal human males given an acute dose of 50 mg of naltrexone reported irritability, dysphoria, sexual ideation and penile erections (Mendelson et al. 1979). Such subjective complaints were not reported by normals given 10 mg of naltrexone increasing gradually to 50 mg over a period of days (O'Brien et al. 1978). These complaints generally have not been reported by thoroughly detoxified postaddicts given gradually increasing doses of naltrexone.

Tolerance appears to develop to these endocrine effects, although, thus far, human subjects on long-term naltrexone have not been adequately examined for chronic endocrine effects. Most of the speculation concerning chronic disruption of the endorphin system in human subjects is supported by anecedotal evidence only. For example, one might expect pain systems to be affected in the direction of a lowered threshold. However, we have been impressed by the reactions of two long-term naltrexone patients who sustained trauma and demonstrated a higher than normal tolerance for pain. There is also reason to suspect from animal studies that feeding behavior may be affected (Morley 1980). A few clinicians have also reported cases of apparent naltrexone-related appetite suppression. However, a review of the large NAS/NIDA series of naltrexone patients reveals about an equal number of those who gain and lose weight (Bradford and Kaim 1977).

One might also expect some direct effects of naltrexone on the homeostatic equilibrium of the endorphin system. Zukin and colleagues (1981) have reported increased sensitivity of rat brain opioid receptors beginning within the first two days of naltrexone treatment and increasing for eight days thereafter. In postaddict humans treated for two to eight weeks with naltrexone, we have reported increased endorphin activity as measured by radioreceptor assay (O'Brien et al. 1981). However, this can only be considered a preliminary report because the magnitude of this increase is uncertain due to difficulties in

extracting all of the naltrexone metabolites which themselves were active in the receptor assay.

Several studies have reported a possible effect on "craving," but this has not been satisfactorily separated from the setting variable, that is, the presence or absence of drug availability.

The bottom line on safety is that this is a powerful drug with widespread effects; yet, by all of the usual criteria, it appears remarkably safe.

EFFICACY

Pharmacological efficacy is a straightforward question and the answer is equally straightforward. Naltrexone clearly acts as a competitive antagonist of opioid drugs (Martin et al. 1976). When a subject is "protected" by naltrexone, the effects of opioids are blocked or attenuated in a dose-related fashion. Significant antagonism can persist for 72 hours after a 150 or 200 mg dose of naltrexone (Resnick et al. 1974, O'Brien et al. 1975) . The degree of antagonism is related to the plasma levels of naltrexone and its active metabolites, and thus it is less in patients who are rapid metabolizers (Verebey 1980). Under controlled laboratory conditions some opiate effects can be perceived by subjects injecting opioids while receiving naltrexone, and these have been confirmed by physiological monitoring devices in two laboratories (O'Brien et al. 1975, Verebey 1980). However, the attenuation is such that even fairly large street doses of heroin are relatively non-rewarding. Thus, it is practical to give naltrexone two or three times per week and assume that the patient will be wasting money if he uses street heroin. For perhaps the first time in many years, a detoxified former addict is free to walk the streets of his neighborhood without fear of becoming re-addicted.

So, the pharmacological efficacy of naltrexone is unquestioned. What about clinical efficacy? This is a complex question which involves hard-to-define issues such as readiness for opioid-free treatment, patient goals vs. therapist goals, and availability of other reinforcers such as employment. Perhaps the most difficult question involves the technology to test the clinical efficacy of an antagonist drug.

We are accustomed to using a double-blind trial of test drug vs. placebo. Such trials have already demonstrated the clear pharmacological efficacy of naltrexone in short-term inpatient studies (Meyer et al. 1976). Clinical efficacy in a placebo controlled trial is a different matter. The structure of such a trial is based on naltrexone's known pharmacological activity. Patients are told that they will receive either an antagonist or placebo. If they test by using opioids, they can "break" the blind. If they fail to test, then placebo has, in

a sense, "borrowed" naltrexone's pharmacological activity and there is no advantage to being on naltrexone. In fact there is an advantage to being on placebo because placebos have no possible pharmacological side-effects.

The results of the one large placebo-controlled trial of naltrexone follow this pattern (Hollister et al. 1978). Overall there were no differences between placebo and naltrexone. Among the small sub-sample who tested the blockade, there was a significant advantage for naltrexone. Those on naltrexone tested once or twice at the beginning and then stopped illicit drug use. Those on placebo continued to test intermittently throughout the trial.

What then is the clinical role of naltrexone? Our review of the literature and nine years of clinical experience with naltrexone indicate that it is an important option for perhaps 5-10% of opioid addicts at a given time in a large multi-modality treatment program. Patients who have done well on methadone maintenance and who have undergone a planned slow detoxification are good candidates. Retrospective analyses have shown that those who have stable relationships and employment are more likely to do well (Resnick et al. 1979). Former addicts who have served a prison term, particularly those in a work-release program have done well (Brahen et al. 1977). Physician addicts have done exceptionally well on naltrexone. Patients receiving psychotherapy, family therapy or behavior therapy have generally done better than naltrexone patients not getting these treatments (Grabowski et al. 1979, Anton et al. 1981, Resnick et al. 1981). Long term follow-ups have generally shown that the longer the patient remains on naltrexone in the community the greater the likelihood of finding that patient opioid-free at one year follow-up. While naltrexone blocks only opioid effects, only a few patients show increased use of alcohol and other drugs.

Of course, skeptics can appropriately point out that those who continue on naltrexone are relatively good prognosis patients anyway and that you may get equally good results by giving placebo naltrexone. This is probably true, at least as long as some patients in the population were receiving active naltrexone so that the antagonist treatment structure and reputation would be maintained. If naltrexone were made totally unavailable, so that all patients received placebo, the word would eventually get out. The results then would be no different from drug-free outpatient therapy, which has even less compliance than antagonist programs.

In our opinion, the release of naltrexone for general use is long overdue. We realize that there are certain problems with drugs used in a small specialized population, the so-called "orphan" drugs. Unless new indications are found for naltrexone, such as the treatment of certain types of obesity,

there is unlikely to be much financial profit in this drug. However, there will be a great loss to the addiction treatment field if it is not approved.

Another promising agent in the antagonist category is buprenorphine. This is a mixed agonist/antagonist with maximum agonist effects equivalent to about 20 mg of parenteral morphine (Jasinski et al. 1978). Although it has not yet been tested in an outpatient addiction treatment program, preliminary inpatient studies are promising. Buprenorphine may overcome the major problem with naltrexone, which is the lack of compliance. Patients generally like buprenorphine, although they do not report withdrawal effects if they stop it. Perhaps buprenorphine could play a transitional role in a gradual progression from street heroin to methadone to buprenorphine to naltrexone and finally the drug-free state. Of course buprenorphine has its own set of potential problems. It must be given parenterally or sublingually. Its agonist effects give it a certain abuse potential reminiscent of pentazocine. Potential abuse is further influenced by its expected widespread usefulness as an analgesic. The seriousness of the current pentazocine problem ("T's and Blues") makes it mandatory that all agonist/antagonists be carefully considered from this perspective.

In conclusion, the increased sophistication of treatment in the area of substance abuse is reflected in the complexity of the opioid antagonist issue. No longer is it meaningful to say that a treatment was tested in a group of "addicts" or "alcoholics." All addicts are not alike. We must specify the relevant characteristics of the population and the setting. Some patients do well in a particular type of treatment (McLellan et al. 1982). Others get no benefit or may even be made worse by a specific treatment. Data on this concept of matching patients are contained in a paper presented at this meeting by McLellan and colleagues (1982).

Clearly, we have progressed far from the stage mentioned by Dr. Dole in his 1982 Eddy acceptance address when he referred to the time when the only treatment available for addiction was incarceration. We now have many active treatments and although we have a lot further to go in developing better treatments, we have an even further way to go in making these treatments available to the appropriate patients.

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Progress Report: Medical College of Virginia—Sigma Agonists

L. S. Harris, M. D. Aceto, R. L. Balster, and B. R. Martin

Based on an immense amount of chemical and pharmacologic information both in animals and man, Martin and his colleagues (Martin et al., 1976) proposed a concept of multiple opiate receptors. From their own work, they described three receptor types. These were: mu, for morphine-like; kappa, for ketocyclazocine-like; and sigma, for SKF 10,047(N-allylnormetazocine). Since then, the concept of a mu receptor has been extensively investigated (Goldstein et al., 1971). The discovery of stereospecific binding sites in the brain and other tissues led to the identification of endogenous ligands subserving pain and other mechanisms (Hughes, 1975; Chau, 1982).

More recently, attention has focused on possible kappa-type receptors and some progress in this area appears to be forthcoming. In addition, attention is turning to investigations of sigma-type activity. SKF 10,047, the prototypic drug of this type, has a pharmacology quite similar to nalorphine. Thus, it is a mixed agonist-antagonist analgesic which is associated at elevated doses, with a high incidence of nalorphine-like psychotomimetic activity in man. This type of side effect has been one of the limiting factors in the development of better therapeutic agents from this class of compound. Our interest in sigma-like activity was rekindled from a body of work appearing from our laboratory and others which showed a relationship between the pharmacological properties of the sigma agonists and phencyclidine (PCP). This information is summarized in Table 1.

Of particular interest was our finding (Brady et al., 1982) that there may be some stereoselectivity to sigma-like activity. Thus, in drug discrimination studies, (±)-SKF 10,047 generalized to PCP while the (-)-isomer did not at doses below those which produced behavioral disruption. We have later shown that animals can be trained to discriminate (+)-SKF 10,047 from vehicle, and that PCP is generalized to this discriminate cue while the (-)-isomer does not at doses below those which produce behavioral disruption (Balster and Brady, In press). Thus (+)-isomer of SKF

10,047 is more specific for PCP-like effects. The (-)-isomer, and therefore, the racemate, have prominent non-PCP-like effects probably mediated by mu or kappa receptors which may mask sigma activity.

Table 1

REPORTED SIMILARITIES BETWEEN PCP AND THE SIGMA-AGONIST (±)-N-ALLYLNORMETAZOCINE (SKF 10,047)

1. Similar Effects in the Chronic Spinal Dog

   Jasinsky et al., 1981
   Martin et al., 1976

2. Receptor Binding Studies - Displacement of Bound PCP or SKF 10,047 by SKF or PCP, Respectively

   Palmur et al., 1980
   Quirion et al., 1981
   Zukin and Zukin, 1979, 1981

3. Discrimination Studies - Generalization Between Phencyclidine or Ketamine and (±)-N-Allylnormetazocine

   Brady et al., 1982
   Holtzman, 1980
   Shannon, 1981
   Young, et al., 1981

4. Reported Psychotomimetic Effects in Humans

   Davies and Beech, 1960
   Domino and Luby, 1981
   Keats and Telford, 1964
   Martin et al., 1965

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The findings from the discrimination studies prompted us to undertake binding studies. We hypothesized that binding of (+)-SKF 10,047 would be a more homogeneous sigma-like class of receptors than would the binding of the (-)-SKF 10,047. Binding of the latter should be more readily displaced by mu and kappa agonists or antagonists. It is preliminary results with binding of the isomers of SKF 10,047 that are described here. First, radiolabeled (+)-SKF 10,047 with high specific activity had to be prepared. This was done by preparing the pure isomers of N-propargylnormetazocine and reducing them with ^{3}H (Figure 1). The ^{3}H reduction was carried out by Dr. F. I. Carroll at the Research Triangle Institute. This gave the (±)- and (-)-isomers with a specific activity of ^{54}Ci/mmole and ^{65}Ci/mmole, respectively.

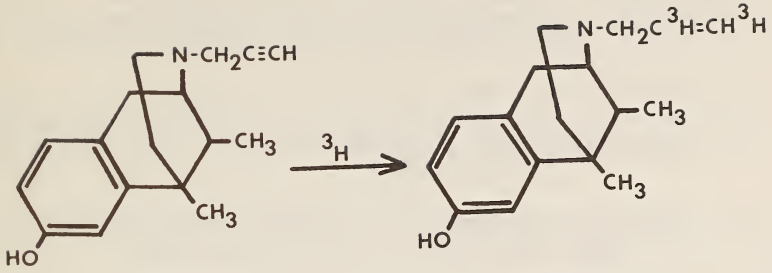

Figure 1

Binding studies using rat brain homogenates with labeled dehydromorphine as the ligand, showed that (-)-SKF 10,047 displaced with a K_1 = $1x10^{-10}$ $M_{.5}$ while the (+)-isomer produced only a 67% displacement at 10^{-5}M. Using the labeled SKF 10,047 isomers and rat brain homogenates, linear Scatchard plots were obtained for both isomers. The (-)-isomers had an estimated K_D = 1.2 x 10^{-8}M.

Using other ligands, we found that (-)-morphine displaced the (-)-SKF 10,047 but not the (+)-isomers while (+)-morphine displaced (+)-SKF 10,047 25 times more effectively than (-)-SKF 10,047. Displacement studies with a wide variety of other ligands are now in progress. Sodium chloride did not effect the K_D of either (+)- or (-)-SKF 10,047. However, the number of binding sites of (-)-SKF 10,047 was markedly reduced by the addition of NaCl.

We also took the opportunity to reexamine the agonist and antagonist activity of (±)-, (+)-, and (-)-SKF 10,047 in a variety of antinociceptive test procedures. Neither (±)-SKF 10,047 nor its isomers were active as antinociceptive agents in the tail-flick test. In the phenylquinone abdominal stretching (PPQ) test, the racemate was about 50 times less potent than morphine (see Table 2).

Table 2

AGONIST ACTIVITY OF SKF 10,047 AND ITS ISOMERS

Compound	Tail-Flick Agonist ED_{50} mg/kg	PPQ Abdominal Stretching Test ED_{50} mg/kg
Morphine	5.8	0.23
(±)-SKF 10,047	Inactive to 30	10.4
(+)-SKF 10,047	Inactive to 30	Inactive to 40
(-)-SKF 10,047	Inactive to 40	1.3

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The (-)-isomer gave an ED_{50} = 1.3 mg/kg while the (+)-isomer was inactive in doses up to 40 mg/kg. Thus, there was a separation of greater than 40 to one between the (-)- and (+)-isomers as agonists. As antagonists, the racemate was active against morphine in both the tail-flick and PPQ tests (see Table 3).

Table 3

ANTAGONIST ACTIVITY OF SKF 10,047
AND ITS ISOMERS

Compound	Tail-Flick Antagonist ED_{50} mg/kg	PPQ Test Antagonist ED_{50} mg/kg
Morphine	N/A	N/A
(±)-SKF 10,047	1.9	3.3
(+)-SKF 10,047	13.2	Inactive to 30.0
(-)-SKF 10,047	0.2	1.2

########

The antagonist activity lies essentially in the (-)-isomer. The separation in the tail-flick test was greater than 60 to one; while in the PPQ test, the (+)-isomer was inactive in doses up to 30.0 mg/kg, giving a ratio of at least 30 to one. Thus, except for some very weak antagonist activity in the tail-flick test, (+)-SKF 10,047 appears to have little narcotic agonist or antagonist activity. In other experiments we found that naloxone was able to antagonize the antinociceptive activity of (±)- and (-)-SKF 10,047 in the PPQ test. However, it takes 30 times more naloxone to antagonize the racemate than the (-)-isomer.

In summary, we have found many pharmacological commonalities between the sigma agonists SKF 10,047 and PCP with evidence that the (+)-isomers has more selectivity for PCP-like effects.

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Progress Report From the NIDA Addiction Research Center (Preclinical Laboratory), Lexington, Kentucky

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First, a brief administrative update. In this transition period (during which the ARC is in process of relocating from Lexington, Ky. to Baltimore, Md.) a unit of the ARC remains active in Lexington, engaging primarily in animal and chemical research, but also working coordinately and collaboratively with our colleagues in Baltimore. We are anticipating at this time that final relocation will be accomplished in the summer of 1984. In my progress report I will highlight briefly the results of several ongoing studies in our laboratory.

METABOLISM OF OXYMORPHONE

This study is being performed in the Chemistry Section and describes the metabolism and urinary excretion of oxymorphone in man and several laboratory animals. This is part of a study which was undertaken several years ago to study the comparative metabolism of six compounds which had in common a ketone at the no. 6 position. Naloxone and naltrexone are narcotic antagonists. Oxycodone (in Percodan), hydromorphine (or Dilaudid), and oxymorphone (or Numorphan) are strong analgesics; and hydrocodone (in Hycodid) is used primarily as an antitussive. Although these drugs have been used for many years, there was little known of their metabolism or urinary excretion profiles.

In the human study, single 10 mg. oral doses of oxymorphone hydrochloride were administered to six healthy, adult male, Federal prisoners from whom informed consent had been obtained. All were former addicts who were drug free at the time of the study. Control urines were collected for 24 hr. prior to drug administration; and following drug, all urine was collected for 144 hr., with collection periods ending at 2, 4, 8, 12, 24, 48, 72, 96, 120 and 144 hr.

In the animal studies, the following species were used: Male albino Wistar rats (N = 6); male albino New Zealand rabbits (N = 4); male albino Hartley guinea pigs (N = 4); and one male and one female mongrel Beagle dog. Each subject received a single

2.5 mg./kg. dose of oxymorphone hydrochloride, administered subcutaneously. Urine was collected for 24 hr. predrug and 24 hr. following drug administration. Urine samples were frozen until the time of analysis.

Standard extraction and acid-hydrolysis procedures were used for isolation of oxymorphone and metabolites. Briefly, samples were extracted for free or total drug at pH 10 with chloroform/isopropanol (9:1 v/v), back-extracted into acid, and basified and reextracted with chloroform/isopropanol. Following evaporation, samples were converted into silyl derivatives for GC and GC/MS analysis. Recovery of oxymorphone by this procedure was 73.4 percent.

Oxymorphone was found to be excreted in small amounts in the intact form, as well as being extensively conjugated at the 3-phenolic position. In addition, metabolites of oxymorphone were isolated which were identified by comparison with authentic standards as 6-ketone reduction products, i.e., 6β-oxymorphol and 6α-oxymorphol. No noroxymorphone was detected.

A quantitative assay for oxymorphone and its 6-keto reduced metabolites was developed with GC/MS-mass fragmentography, using methane chemical ionization mode, with 6β-hydrocodol as internal standard. Linear standard curves were obtained from 0.1-2.0 μg./ml. for oxymorphone and from 0.05-1.0 μg./ml. for the metabolites. Samples were analyzed in triplicate.

In the six human subjects, total oxymorphone excretion over the 6-day collection period ranged from 28 to 57 percent of the administered dose, with a mean of 41 percent. Small amounts of 6β-oxymorphol were found (about 3 percent of the administered dose), together with traces of 6α-oxymorphol. This pattern of 6-keto reduction (i.e., selectivity for the 6β configuration) is consistent with that found for other 6-keto opioids possessing a 3-phenolic group (i.e., naltrexone, naloxone, and hydromorphone). Both oxymorphone and its metabolites were extensively conjugated (i.e., greater than 90 percent). Overall urinary recovery of the administered dose ranged from 30 to 60 percent.

Results of the animal studies from this and previously presented data from this study allow several cross-species generalizations. There was very little 6-keto reduction in the rat and dog, while guinea pig and rabbit produced about the same amounts as did man. This is consistent with previous studies. With regard to stereoselectivity, man and rabbit produced predominantly the 6β form, while guinea pig showed predominantly 6α. Again, this is a consistent pattern; the guinea pig generally shows the lowest β/α ratio, but this is the first compound where it has been less than 1 in these *in vivo* studies. All species but the rabbit showed a heavy preponderance of conjugated urinary metabolites. Generally, the dog has always shown strong conjugation, with man strong to intermediate. The rat and guinea pig have varied somewhat from drug to drug; and the rabbit has been a consistently poor

conjugator. Overall drug recovery ranged from about 15 to 90 percent. In these studies, recovery has been consistently low in the rat, moderate to high in man and guinea pig, and somewhat variable in dog and rabbit.

The data from this study should prove useful in further defining cross-species differences and similarities and for predicting likely oxymorphone metabolites and amounts detectable in human urine following use or possibly abuse of this compound.

SKF-10,047 EVALUATION IN THE DOG

This study is from the Whole Animal Pharmacology Section and concerns our continued interest in the relationship of σ-opioid receptor agonists and PCP. The similarity between PCP and N-allylnormetazocine (SKF-10,047, NANM) has been reported in several animal species including rat, dog, and squirrel and rhesus monkey. Although initial studies evaluated primarily racemic SKF, more recent studies (and those reported here) have focused on the pharmacology of the stereoisomers. Specifically, this study was aimed at determining if the PCP-like activity of SKF resided in one of the two stereoisomers, thereby demonstrating a pharmacologic selectivity of action. For this purpose, the spectrum of action and relative potencies of the d- and l-isomers of SKF, the racemate, PCP, and saline were determined in two groups of three chronic spinal dogs using an incompletely randomized crossover design, with geometrically spaced doses. Subjects were adult, female Beagle dogs, with chronic spinal section at T-10, who had been off all chronic drugs for at least 6 months prior to initiation of the study. The study is now half completed and the results obtained in the first three dogs are presented. The experimental paradigm utilized a 30-min. control period, followed by the intravenous administration of the drug over 4 min., and a 60-min. postdrug observation period. Parallel line bioassay analyses of variance were employed to evaluate physiologic effects measured as 60-min. areas of the time-action curves and behavioral effects reported as total 1-hr. scores.

Profiles of action for PCP and racemic SKF have been established previously in the dog. Common effects of these two compounds were depression of the flexor reflex, tachycardia, mydriasis, retraction of the nictitating membrane, analgesia (as indicated by increased onset latency of the skin twitch reflex), hyperthermia, and the combination of nystagmus and stereotypy.

Comparison of d- and l-SKF in the present study showed that both isomers produced dose-related depression of the flexor reflex, augmentation of the pulse rate and of skin twitch reflex latency, dilatation of the pupils, increases in the incidence of concurrent nystagmus and stereotyped head movements, and increase in whining. Also, increases were seen in respiration, temperature, and incidence of staring. At the highest dose tested, all of the dogs at one time or another failed to attend to external stimuli. Among the potency estimates, only the mydriatic response produced

confidence limits that did not include 1; for this measure the d-isomer appeared somewhat more potent than the 1-isomer. Also, it appeared that the 1-isomer more effectively depressed the flexor reflex than did the d-isomer, but confidence limits could not be calculated because of preparation differences. A lower dose of the 1-isomer is being added to the study. The effects of the racemate and PCP were identical to those observed for the individual SKF isomers. The dose-response curves of the racemate were located in close proximity to or between those of the isomers. With one exception, the PCP curves were positioned to the left of the three SKF curves by 0.5 to 1 log unit, indicating a greater potency of PCP than racemic SKF or its individual isomers. For the flexor reflex, the PCP curve was partially superimposable on the curve for 1-SKF.

In summary, it is tentatively concluded that both the d- and 1-isomers show pharmacologic activity of the σ type, indicating no selectivity of action, with both profiles similar to that of PCP. In addition, the isomers are generally equal in potency; although the 1-isomer was less effective as a mydriatic and possibly depressed the flexor reflex more than the d-form. These two exceptions could suggest a slightly higher degree of κ activity associated with the 1-isomer of SKF.

NICOTINE AND COCAINE SELF-ADMINISTRATION IN THE DOG

This study, from the Behavioral Pharmacology Section, is a follow-up on the continuing exploration of the reinforcing properties of nicotine in comparison with cocaine in the dog. Subjects of this study were four Beagle dogs surgically fitted with venous catheters, then given access to response-contingent drug infusions under a fixed-ratio with limited hold schedule of reinforcement. Daily sessions, conducted Monday through Friday, consisted of 16 trials, each trial lasting a maximum of 10 min. During each trial, the 15th lever-pressing response produced a 15-sec. i.v. infusion of drug (i.e., an FR-15 schedule). Successive trials were separated by a time-out period, lasting at least 240 sec. Following acquisition of stable responding (with cocaine as the reinforcer), the dogs were tested with five doses of nicotine (3-300 µg./kg./infusion), five doses of cocaine (3-300 µg./kg./infusion), and saline. Each dose was tested for five to seven consecutive sessions, with treatment order randomly determined for each dog.

Results of the first study showed that both nicotine and cocaine were self-administered above saline levels, with the maximum number of infusions occurring at doses of 30 and 100 µg./kg./infusion. For both drugs, overall response rates varied systematically as a function of dose per infusion, with nicotine reaching a maximum of 0.3 responses/sec. at 30 µg./kg./infusion and cocaine with a maximum of 0.7 responses/sec. at 10 µg./kg./infusion. The running rate also showed systematic variation with dose with maximum rates at 10 µg./kg./infusion for both drugs.

Upon completion of the dose-response curves, the effects of presession treatment with the nicotinic antagonist mecamylamine on nicotine and cocaine self-administration behavior were assessed in the same four dogs. Mecamylamine, at a dose of 1 mg./kg., i.v., was given 30 min. before the start of each session for seven consecutive sessions; both nicotine and cocaine were administered at a dose of 30 µg./kg./infusion. For both infusions per session and overall response rate, presession treatment with mecamylamine altered the behavior maintained by nicotine, but not the behavior maintained by cocaine. The number of nicotine infusions per session dropped from 13.9 during the control period to 11 on the first session of mecamylamine treatment and continued to decline over the 7-day period to 4.7 infusions. Similarly, the overall response rate dropped to 34.5 percent of control in the first mecamylamine pretreatment session and continued to decline to 7 percent of control after 7 days of mecamylamine. When responding was maintained by cocaine infusions, presession treatment with mecamylamine had little effect on the response rate and no effect on the number of infusions self-administered each session. The temporal pattern of nicotine self-administered during mecamylamine treatment was much like that seen when saline was substituted for drug. The first two or three fixed-ratio trials in each session were rapidly completed, resulting in two to three infusions separated by the shortest possible time-out period. If any subsequent infusions occurred, they were separated by long periods of minimal, if any, responding. During mecamylamine treatment, the temporal pattern of cocaine self-administration was unchanged.

In summary, it is concluded that nicotine does have reinforcing properties demonstrable in the laboratory; and they appear to be due to a mechanism involving nicotinic receptors and different from that of cocaine.

BENZODIAZEPINE ANTAGONISTS

This study, also from the Behavioral Pharmacology Section, concerns benzodiazepine antagonists. As the sedative-hypnotics have become of greater concern as drugs of abuse, emphasis on these compounds has increased in studies at the ARC and major studies have been initiated in this area. This paper summarizes initial results of studies on two benzodiazepine antagonists: Ro 15-1788, an imidazodiazepine derivative which has been reported to selectively antagonize the effects of benzodiazepines in humans and animals; and CGS 8216, a pyrazoloquinoline derivative reported to antagonize the anticonvulsant effects of diazepam (although CGS may also antagonize nonbenzodiazepine sedative-hypnotics). In these studies, the discriminative stimulus paradigm in the rat was used. Male, Fisher-derived rats were trained to discriminate between saline and either 1.0 or 3.0 mg./kg. of diazepam s.c. in a two-choice, discrete-trial, shock avoidance or escape procedure by responding on one lever after receiving saline and on a second lever after receiving diazepam. Each session consisted of 20 trials or 30 min.; data are presented as percent of responses completed on the diazepam appropriate lever. Animals were trained and maintained at a 90 percent correct response criterion.

The effects of CGS and Ro on the discriminative stimulus properties of diazepam and pentobarbital in rats trained to discriminate 1.0 mg./kg. diazepam were evaluated. The antagonists were administered 40 min. before the start of the session (Ro as an oral suspension and CGS i.p.) and diazepam or pentobarbital was administered subcutaneously 30 min. presession. Diazepam and pentobarbital alone produced greater than 85 percent diazepam appropriate responding. Both CGS and Ro produced a dose-related antagonism of diazepam discriminative effects but did not alter the effects of pentobarbital. CGS was approximately ten times more potent than Ro on a mg. for mg. basis. Both antagonists administered alone produced almost exclusively saline appropriate responding. Similar results were obtained in rats trained to discriminate pentobarbital from saline.

The effects of varying doses of Ro on the diazepam dose response curve in animals trained to discriminate 1 mg./kg. diazepam were determined. Ro and diazepam were administered by the same routes in the same time course as described above. Diazepam dose effect curves were shifted approximately three- and 18-fold to the right in a parallel fashion by 10 and 32 mg./kg. of Ro. Preliminary data indicate that CGS produces similar parallel shifts in the diazepam dose effect curve.

In another set of experiments, interactions between diazepam, ethanol, and CGS were evaluated. In this study, cumulative dose response curves were generated in a single session in each subject. Ethanol or tap water was administered 30 min. presession. The session consisted of consecutive 15-min. periods, the first 10 min. of which was a black-out period, followed by a 5-min. period during which a maximum of ten discriminative stimulus trials were run. Diazepam was administered at the beginning of the black-out period in amounts resulting in the cumulative doses of 0.1 to 10 mg./kg. Animals were trained to discriminate 3.0 mg./kg. diazepam. The cumulative latency was also determined, that is, the time from the beginning to the end of each trial summed over ten trials for each point. Ethanol alone at a dose of 1.8 g./kg. administered orally caused no diazepam appropriate responding, but produced an approximately three-fold shift to the left in the diazepam dose response curve; about a ten-fold shift was seen in the cumulative latency dose response curve. That is, ethanol potentiated the discriminative stimulus and latency increasing effects of diazepam. In CGS interaction studies, CGS was administered concurrently with the first dose of diazepam in a dose of 3.0 mg./kg. i.p. CGS produced a greater than 40-fold shift to the right in the dose response curves for diazepam both alone and in the presence of ethanol. These results indicate the potentiating effects of diazepam by ethanol and the effectiveness of CGS in antagonizing diazepam even in the presence of ethanol.

In summary, these initial data seem consistent with the conclusions that Ro and CGS appear to be specific benzodiazepine antagonists, working via a competitive antagonistic mechanism, and they may have potential clinical utility. Studies are presently

underway to further define their specificity and mechanism of action.

AUTHORS

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Progress Report of the NIDA Addiction Research Center, Baltimore, Maryland, 1982

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As reported last year, the Clinical Research Program of the Addiction Research Center (ARC) has been successfully relocated to Baltimore City Hospitals. The first subject was admitted in February 1980. From February 20, 1980 to December 31, 1981 there were a total of 179 volunteer admissions into the ARC clinical unit for research studies. Of these admissions, 108 subjects completed their study, 40 voluntarily withdrew, 24 were discharged for medical reasons, 5 were discharged for adverse behavior and 2 were discharged because of inability to give informed consent.

Review of subject drug histories revealed a wide range of patterns of abuse, from cigarette smoking to poly-drug abuse. Comparison of selected psycho-social characteristics with those obtained in the CODAP survey for corresponding periods, nationally and in Baltimore, indicated that the ARC subject population is similar to that in treatment. These observations suggest that the subject population is appropriate to the type of drug abuse/liability research studies conducted at the ARC.

STUDY I - EVALUATION OF CHLORDIAZEPOXIDE FOR PENTOBARBITAL-LIKE EFFECTS

In the last annual report (Jasinski et al. 1981), we reported that diazepam given in single doses produced typical pentobarbital-like effects including euphoria. The onset, peak and duration were similar for both diazepam and pentobarbital. Relative potencies were similar across subjective and behavioral measures indicating diazepam is 10 times more potent than pentobarbital in producing euphoria and subjective effects. A preliminary study comparing chlordiazepoxide 50, 100 and 200 mg, pentobarbital 120 and 240 mg and placebo was conducted. Chlordiazepoxide produced dose-related pentobarbital-like effects and euphoria; however, the response to the 200 mg dose was less than that of the 240 mg dose of pentobarbital. Consequently, valid bioassays were not obtained; therefore, the study was

repeated with a larger dose of chlordiazepoxide. In this second study chlordiazepoxide 100, 200 and 400 mg pentobarbital 120 and 240 mg and placebo were all given orally and compared in six subjects. The experimental design and procedures were similar to those for the first chlordiazepoxide study and the diazepam study as reported in last year's annual report. It was found that the onset, peak and duration of response of chlordiazepoxide and pentobarbital were similar. Valid relative potencies were obtained on all measures except that for the euphoria scale in which there was a flat dose response curve for chlordiazepoxide. On the basis of the studies conducted to date with both chlordiazepoxide and diazepam, it is concluded that (in the doses studied) diazepam and chlordiazepoxide produced pentobarbital-like effects including euphoria. Diazepam is 10 times as potent as pentobarbital while chlordiazepoxide is 1/2 as potent as pentobarbital. Therefore, by extrapolation chlordiazepoxide is approximately 1/20 as potent as diazepam in producing subjective effects and euphoria. The flat dose response curve for the euphoria scale scores with chlordiazepoxide indicates the possibility of qualitative differences between diazepam and chlordiazepoxide.

STUDY II - ASSESSMENT OF NABILONE AND DELTA-9-TETRAHYDROCANNABINOL (THC) FOR ABUSE POTENTIAL

The cannabinoids nabilone and THC are proposed for introduction into therapeutics as treatment modalities for the nausea and vomiting associated with certain forms of cancer chemotherapy. Although THC has been shown to produce marijuana-like effects, there is no epidemologic evidence to indicate that THC will have an abuse potential equivalent to marijuana smoking. Further, studies by others have indicated that nabilone may produce effects which are distinct from that of THC. A single dose study has been initiated in which ten subjects are being given, according to a latin square design, the following treatment conditions: 1) placebo, 2) morphine, 15 and 30 mg subcutaneously, 3) THC 5, 10 and 20 mg orally, 4) nabilone, 2, 4 and 8 mg orally and 5) on one occassion the smoking of a standard 1-1.5% NIDA marijuana cigarette. Except for the cigarette smoking condition, the studies are conducted under "double-blind" and "double-dummy" conditions. The purposes of the study are to learn if marijuana and THC produce similar subjective, physiologic and behavioral effects and to learn if both are euphoriants compared to the euphoric responses to standard doses of morphine and the standard 1-1.5% marijuana cigarette. The study is not completed; however, a preliminary analysis of the data indicates that when given orally, THC and nabilone produce similar effects. Both are euphoriants as measured by responses on the ARCI MBG and liking scales. It should be noted that oral THC and inhaled marijuana have a more rapid onset of action than nabilone; however, the effects of nabilone last longer than those of THC.

STUDY III - CONTINUATION OF STUDIES OF INTRAVENOUS NICOTINE AND TOBACCO SMOKE

In last year's annual report, we reported that nicotine is a euphoriant when given to addicts either intravenously or in cigarette smoke. Methods had been developed to quantify the subjective, physiologic and behavioral changes produced by nicotine, and a self-administration procedure was developed to conduct behavioral pharmacologic studies of intravenous nicotine in humans. In the past year these studies have continued and have been extended. One major group of studies has been to investigate mecamylamine as a competitive antagonist to the physiologic, subjective and behavioral effects of nicotine. These studies will be reported in greater detail in another chapter in this volume (Henningfield, Miyasato and Jasinski). In addition, we have continued self-administration studies for the purpose of comparing and integrating the findings in man with those of animal studies concerned with the reinforcing effects of nicotine, predominantly those of Dr. Steven Goldberg in our laboratory. Further, we have been interested in investigating the relation of nicotine-induced euphoric and dysphoric responses to the self-administration behavior and in investigating the role of tolerance development in nicotine. When given access to two levers, one resulting in the injection of saline and the other resulting in injection of nicotine over a range of dosages, subjects self-administer nicotine in preference to saline. Studies of the euphoric responses to programmed injections of nicotine indicate that tolerance develops rapidly to nicotine. This suggests that in self-administration studies involving repeated administration of nicotine (and by extrapolation cigarette smoking) the positive effects of the nicotine are rapidly lost through tolerance. It's probable that with short periods of abstinence, the reinforcing effects are rapidly recovered. In series of self-administration studies, subjects rated the degree of positive responses to nicotine in an analogue scale after each self-administration of nicotine. In addition, after the three-hour self-administration session they were required to give their overall liking for the drug effect in the session. Increasing doses of mecamylamine reduced the liking score, the self-administration and positive analog scale responses in direct proportion to the dose of mecamylamine.

Our studies to date with nicotine delivered either intravenously or in tobacco smoke have led us to conclude that (1) nicotine can act as a reinforcer in humans relative to placebo, 2) that tolerance to nicotine is rapidly developed and lost, 3) that self-administration behavior is related to the perceived positive and negative effects of nicotine. The relation between self-administration and perceived positive and negative stimulus strength is complex but orderly. Finally, the biomedical and behavioral data generated to date justifies the investigation of chemotherapy as an approach to treating tobacco addiction.

STUDY IV - STUDIES OF BUPRENORPHINE AS A TREATMENT AGENT IN NARCOTIC ADDICTION

In previous meetings we reported that the long-acting partial agonist of morphine, buprenorphine, produced little or no physical dependence and had proposed that buprenorphine might have utility as a treatment drug in narcotic addiction. At last year's meeting we reported on a series of single dose studies evaluating the sublingual and oral route and had concluded that given orally in doses of 10 to 40 mg, sublingually in doses of 2-4 mg, and subcutaneously in doses 1 to 2 mg, buprenorphine could act as a maintenance/detoxification agent. In the past year we have conducted studies by both the subcutaneous and sublingual routes of administration on the use of buprenorphine as a detoxification maintenance agent. At this meeting we will report on only our experience evaluating buprenorphine as a detoxification agent for methadone maintenance patients. Our studies have emphasized detoxification in methadone maintenance patients primarily because this has allowed us to use volunteers with known levels of physical dependence. It is also felt that the most difficult narcotic detoxification is that of methadone and because of its long-lasting withdrawal syndrome, it could serve as the prototype for other detoxifications. Finally, a major therapeutic problem in treating narcotic addiction is the disruption caused by the discontinuation of methadone in a patient who has exhibited psychosocial rehabilitation with maintenance, and as such buprenorphine may have an immediate utility.

As a partial agonist, under certain conditions buprenorphine was shown to be able to precipitate abstinence. To determine if in doses proposed for maintenance/detoxification buprenorphine would precipitate abstinence, a series of studies were done in six subjects dependent upon methadone. Maintenance levels of methadone were 25 mg, 30 mg, 2 subjects at 40 mg and 2 subjects at 45 mg for a mean methadone maintenance dose of 38 mg. Using our standard precipitated abstinence procedure, under "double-blind", "double-dummy" conditions, subjects were tested twice weekly with test doses being given three hours following the subject's methadone maintenance dose. Test doses of placebo, naloxone 0.5 mg subcutaneously, and buprenorphine 2 and 4 mg sublingually, were given in randomized order.

When compared to placebo, naloxone produced physiologic signs of withdrawal that include pupil dilation, increased blood pressure, lacrimation, rhinorhea, perspiration and subjective reports of withdrawal sickness. Buprenorphine, on the other hand, produced mydriasis and hypertension; however, there were no subjective reports of withdrawal sickness. Subjects did report with two doses of buprenorphine feelings of relaxation, coasting and typical opiate-like subjective effects in contrast to naloxone in which the primary symptoms were nervousness and upset stomach. These observations suggest that there is lack of cross tolerance

in methadone maintenance patients to some of the effects of buprenorphine. In addition, there is no evidence that, in methadone maintenance patients (up to 45 mg), buprenorphine will precipitate clinically significant withdrawal.

A series of studies was conducted to determine if buprenorphine would substitute for methadone such that the withdrawal from the substituted buprenorphine would be less than that expected from the methadone. The first set of experiments were concerned with the transition from methadone to buprenorphine and the second set with abrupt withdrawal of substituted buprenorphine. Both sets of experiments were conducted under double-blind conditions with subjects residing on the ARC ward with daily monitoring of signs of abstinence, signs of intoxication and subject's and observer's chronic opiate questionnaires and the items from the weak and strong opiate withdrawal scale of the Addiction Research Center.

In the first set of transition experiments eight subjects on methadone (25 mg in two subjects, 30 mg in one subject, 40 mg in three subjects and 45 mg in two subjects for a mean of 36 mg) were abruptly transferred from methadone to a 2 mg daily sublingual dose of buprenorphine given under double-blind, double-dummy circumstances. Subjects perceived the change, reported mild discomfort, which reached its maximum following the third day of substitution; however, by the fourth and fifth day the subjects were stabilized.

A second group of four subjects were transferred from methadone to 2 mg of sublingual buprenorphine under identical circumstances except that after the administration of the daily sublingual buprenorphine, methadone administration was continued in an attempt to attenuate even the mild withdrawal symptoms.

In these subjects on methadone (25 mg, 50 mg in two subjects, and 60 mg in one subject for a mean of 46 mg) the methadone was decreased 50% on the first day of substitution of buprenorphine and 50% every third day until the final dose of methadone was 12.5 or 7.5 mg. When the subject reached this level, methadone was discontinued. It was observed that the continuation of methadone did not attentuate the mild opiate withdrawal signs and symptoms seen during the abrupt transition. It was observed that the symptoms and signs of withdrawal were equal or slightly greater than those seen in the gradual and abrupt transition. This suggests that certain actions of methadone are unrelated to the effects of buprenorphine.

Once stabilized on buprenorphine, subjects reported little or no subjective effects and in general were less sedated than on methadone. Six subjects completed the double-blind study which included 28 days of buprenorphine administration (2 mg sublingually q. day) and the abrupt substitution of placebo under

"double-blind", "double-dummy" conditions. These six subjects originally had been methadone dependent on 40 mg and 45 mg (two subjects each), 25 mg and 30 mg (one subject each) for a mean daily dose of 35 mg. When the substituted burprenorphine was abruptly discontinued, a mild abstinence syndrome was observed on the first day of substitution reaching its peak on the second and third day and then subsiding such that by the fourth day after abrupt discontinuation there were little or no signs of symptoms of withdrawal. The withdrawal after termination of the substituted buprenorphine was different than that of abrupt withdrawal of methadone since methadone withdrawal becomes maximum the third day and persists for weeks. It was hypothesized that the buprenorphine when substituted for methadone would suppress the signs and symptoms of methadone withdrawal but that the basic process of methadone withdrawal was ongoing. Consequently, it was felt that the termination of the substituted buprenorphine led to a re-emergence of the methadone abstinence syndrome. To evaluate this hypothesis, the withdrawal seen from day 29 through 38 following abrupt withdrawal from buprenorphine was compared with previous data for days 29 through 38 following abrupt withdrawal form methadone. Comparison of the abstinence scores and withdrawal signs and symptoms showed that the two syndromes were similar in both degree and intensity, supporting the concept that the abstinence after abrupt discontinuation of the substituted buprenorphine was due to a re-emergence of the methadone withdrawal syndrome. If this hypothesis is true, then it was felt that a longer time of substitution of buprenorphine for methadone should be accompanied by less intense withdrawal or "reversed dependence." A study was conducted in which one subject dependent upon 45 mg methadone daily was placed on "double-blind" "double-dummy" condition on 2 mg of buprenorphine subcutaneously. After fifteen days of buprenorphine administration, placebo was substituted and an abstinence syndrome of increasing intensity developed over the next ten days such that the subject was reporting moderate to severe withdrawal. Administration of buprenorphine 2 mg subcutaneously daily was reinstituted on day eleven and continued for an additional fourteen days such that the second abrupt discontinuation of buprenorphine took place 40 days after the last dose of methadone. Again, abstinence emerged but it was mild and low in intensity lasting for about three or four days and the subject was reporting no withdrawal symptoms ten days later.

On the basis of these studies it is concluded that buprenorphine will partially substitute for methadone. Buprenorphine treatment attenuates the methadone withdrawal syndrome. As a result, buprenorphine can be used to detoxify methadone-dependent patients with minimal discomfort or behavioral disruption. It is possible that buprenorphine and methadone act through separate subpopulations of mu receptors. Finally, the time course of methadone withdrawal appears to be independent of the presence of buprenorphine.

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Testing Drugs for Abuse Liability and Behavioral Toxicity: Progress Report From the Laboratories at the Johns Hopkins University School of Medicine

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A. Introduction

Although this is the first formally constituted progress report from the drug abuse liability assessment laboratories at The Johns Hopkins University School of Medicine to be included in the published proceedings of the Committee on Problems of Drug Dependence Annual Scientific Meeting, the programs supporting this work have been in existence for well over a decade. The animal behavioral pharmacology laboratories at the Johns Hopkins University School of Medicine were established in the early 1970's with funds provided by the Drug Enforcement Agency (DEA) and the National Institute on Drug Abuse (NIDA). Continuing support from NIDA has provided for a vigorous ongoing research program with laboratory baboons focused upon both drug self-administration procedures and senory-motor psychophysical methodologies to evaluate the reinforcing properties and behavioral toxicology of drugs with abuse potential.

B. Progress Report from The Johns Hopkins University School of Medicine Behavioral Pharmacology Laboratories

Research over the past decade or more in the behavioral pharmacology laboratories at the Johns Hopkins University School of Medicine has convincingly demonstrated that there is a good correspodence between the range of chemical compounds self-injected by experimental animals and those abused by humans (Brady et al., 1975; 1976; 1977a; 1977b; Griffiths et al., 1976; 1978; 1981). Moreover, the variables of which such drug self-administration are a function (e.g., dose, response requirement, schedule of availability, environmental conditions, past history, etc.) have been found to exert their influence in a similar fashion independently of the type of substance maintaining the performance or the species of organism involved (Griffiths et al., 1980). The recognition of these cross-species and cross-drug generalities has radically changed conceptualizations of drug-related problems and focused attention upon the need to distinguish between two terms which have continued to be used interchangeably with reference to drug action -- "dependence" and "abuse". Drug dependence has been identified traditionally with the biochemical, physiological, and behavioral

changes which occur acutely and become increasingly manifest following repeated exposure to a pharmacologic agent (e.g., tolerance and withdrawal). Drug abuse, in contrast, defined in the more contemporary context of an extensive self-administration literature, is clearly identified with the characteristically strong drug-seeking and drug-taking behaviors which precede the pharmacological action of abused drugs.

Within the context of these distinctions, the proper preclinical evaluation of a given drug's abuse liability has been considered to require an assessment which takes account not only of the reinforcing properties of the compound in maintaining self-administration, but of its toxic effects as well, in terms of disruptive physiological/behavioral changes. An experimental model has been developed (Brady et al. 1982) for comparing the relative potency of a drug as a reinforcer maintaining self-administration, on the one hand, with its relative potency in eliciting disruptive toxic effects upon sensory and motor functions, on the other, thus providing a potentially useful preclinical assessment of the extent to which self-administration of a drug may involve exposure to the disruptive sensory/motor effects of the compound as a basis for determining its abuse liability.

1. Methods and Results with Animal Drug Self-Administration Procedures

The procedure for determining reinforcing properties with a range of drugs has been previously described in detail (Brady and Griffiths, 1976; 1977a & b; Griffiths, Brady, and Snell, 1978; Griffiths, Brady and Bradford, 1979): Briefly, male baboons (Papio anubis or Papio hamadryas) weighing from 12-30 kg, were adapted to a standard restraint cart, or a harness/tether system (Lukas et al., 1982) and individually housed in a sound-attenuated chamber approximately 0.8 x 0.8 x 1.2 m. Water via a drinking tube and the opportunity to respond for food (1 gram Purina monkey pellets) were continuously available. The food lever was located on the lower right side of a work panel facing the animal, and food pellets were available on a fixed-ratio 30 schedule of reinforcement.

After initial behavioral training on a progressive-ratio paradigm with food reinforcement, each subject was surgically prepared with a chronic silastic catheter in either the internal jugular, femoral, or axillary vein. The catheter was passed subcutaneously, exited at the middle of the back, and was attached to a valve system which allowed for the slow continuous administration (approximately 100 ml/24 hours) of heparinized saline via a peristaltic pump to maintain catheter patency. Drug was injected into the valve system near the animal by means of a second peristaltic pump and then flushed into the animal with saline from a third pump. This system necessitated a delay of approximately 20 sec between onset of drug delivery and actual injection into the vein. All drugs were delivered within a 2-min period. In experiments involving manipulation of drug dose, the volume of drug solution per injection and the injection duration remained constant throughout the experiment.

The availability of a trial occurred at a minimum interval of three hours since the completion of the preceding trial. The availability of a trial was indicated by the illumination of a jewel light directly over the initiate lever located slightly to the left of center at the bottom of the subject's work panel. In the presence of an illuminated jewel light, each response on a standard Lindsley lever produced a brief feedback tone (approximately 0.2 sec). The light remained illuminated until completion of the fixed-ratio requirement (FR 160). At this time, the light over the lever was extinguished, the drug injection began, and a 5 x 5 cm light was illuminated in the upper left hand corner of the intelligence panel for a one-hour period. A time-out period of three hours followed each injection. Thus, a maximum of eight injections was possible each day.

A substitution procedure was utilized to determine whether an unknown compound would maintain self-injection behavior. Self-injection performance was first established with cocaine at a dose of 0.32 mg/kg/inj. After three consecutive days of cocaine availability, during which six or more injections were taken each day, a specified dose of the test drug or saline was substituted for the cocaine. At least twelve days access to each dose of drug or saline was permitted. Cocaine was then reinstated, and when the criterion of three consecutive days of six or more injections per day had been met, another dose or drug was again substituted. The order of exposure to drugs, saline and different doses was mixed; all animals were given twelve days of access to saline several times during the examination of different drugs at different doses. This basic approach thus provided a standardized procedure for evaluating the reinforcing properties of drugs.

A progressive-ratio procedure provided a measure of relative reinforcing strength of a drug by determining the maximum amount of responding (i.e., work) that can be maintained by the compound. Progressive-ratio experiments involved first introducing a drug on the progressive ratio procedure with a low ratio requirement on the initiate lever (usually FR 160) and obtaining a baseline performance of a high and stable frequency of trial completion. Once this performance was established, the ratio requirement on the Lindsley lever was systematically increased until the rate of completing trials fell below a criterion level. A breaking point was defined as the ratio value at which criterion performance disruption occurred. The sequence of ratio values typically included: 160, 320, 640, 1280, 2400, 3600, 4800, 6000 and 7200. Following disruption of performance, the ratio requirement on the Lindsley lever was lowered, and the original performance recovered prior to replication of the experiment or substitution of another dose or drug. The sequence of exposure to different doses of a drug and the order of exposure to different drugs was mixed.

Figure 1 presents illustrative data obtained with the substitution procedure in examining a range of doses of the substituted phenylethylamine, diethylpropion, in one baboon. The figure shows that when saline or a low dose (0.1 mg/kg) of diethylpropion was substituted for cocaine, the self-injection performance decreased during the 12-day substitution period until the

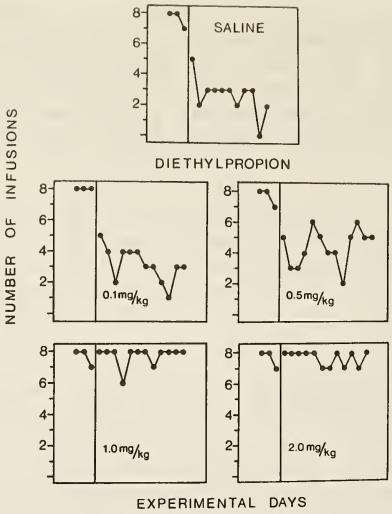

Figure 1. Daily pattern of self-injection maintained by various doses of diethylpropion, HCl and saline in the same subject. The initial three-day period of each determination shows the self-injection performance maintained by cocaine HCl (0.4 mg/kg) prior to substitution of saline or the indicated dose of diethylpropion.

subject self-administered only two or three injections per day. At a dose of 0.5 mg/kg diethylpropion, self-administration performance was maintained at an average rate of about five injections per day, which was higher than saline but lower than the preceding cocaine control periods. Finally, at the highest doses tested of 1.0 and 2.0 mg/kg, the figure shows that relatively stable rates of self-administration were maintained at overall rates comparable to cocaine control periods (seven or eight injections per day).

Figure 2 also presents illustrative data from the substitution procedure showing daily patterns of self-injection performance maintained by saline and several doses of phentermine in three baboons. The figure shows that when saline was substituted for cocaine, the number of injections per day progressively decreased. At a dose of 0.5 mg/kg, phentermine self-injection performance was maintained at levels similar to cocaine control levels. At a dose of 1.0 mg/kg, self-injection performance was also maintained in all three animals, however, drug intake was characterized by a cyclic pattern in which a number of consecutive days of self-injection at a high rate (6 or more injections per day) was followed by several consecutive days at a lower rate and then a return to the higher rate. Previous experiments (Griffiths et al., 1976; Pickens and Thompson, 1971) have documented a virtually identical cyclic pattern of self-injection performance with d-amphetamine.

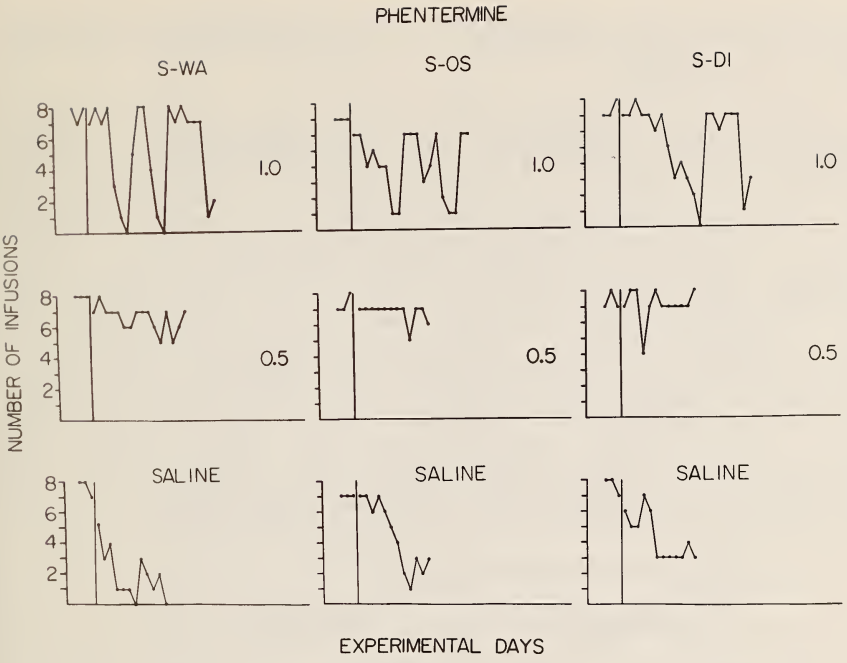

Figure 2. Daily pattern of self-injection maintained by saline or phentermine in three baboons. Ordinates: number of injections. Abscissae: experimental days. Intravenous injections were delivered upon completion of 160 lever presses; a 3-hr timeout followed each injection, permitting a maximum of eight injections per day. The initial three-day period of each determination shows the number of injections maintained by cocaine prior to substitution of saline or indicated dose (mg/kg/inj.) of phentermine.

Figure 3 presents the chemical structure, and Figure 4 the mean levels of self-injection for fourteen phenylethylamines evaluated. As shown in Figure 4, of all the drugs examined, d-amphetamine was the most potent, maintaining levels of self-administration above saline at doses of 0.05 and 1.0 mg/kg. Phentermine, diethylpropion, phenmetrazine, phendimetrazine, benzphetamine, and MDA all maintained levels of self-administration above saline at doses of 0.5 and 1.0 mg/kg. l-Ephedrine, clortermine, and chlorphentermine were the least potent of the drugs which maintained performance, supporting self-injection rates above saline control levels at doses of 3.0 and 10.0 mg/kg (l-ephedrine), 3.0 and 5.0 mg/kg (clortermine), and 2.5 and 5.0 mg/kg (chlorphentermine). In contrast to most of the other phenylethylamines which maintained self-administration behavior, the pattern of self-administration with l-ephedrine was particularly unstable, characterized by either an erratic or cyclic pattern over days. Finally, fenfluramine, PMA, DOM, and DOET were not

self-administered at a rate greater than saline at any of the doses studied (means of the determinations at each dose did not exceed the range of saline values).

A comparison of Figures 3 and 4 provides some information about structure-activity relationships of phenylethylamines. Other laboratory studies (Tessel et al., 1975a & b) have demonstrated that the ability of a series of N-ethylamphetamines substituted at the meta position of the phenyl ring either to increase locomotor activity in mice or to increase isolated guinea-pig atrial rate is inversely related to the meta-substituted steric factor (size). In a subsequent study (Tessel and Woods, 1975), it has been demonstrated that N-ethylamphetamine maintained self-injection performance in rhesus monkeys, whereas fenfluramine (meta-trifluoromethyl-N-ethylamphetamine) failed to maintain self-injection performance. These results indicate that the failure of fenfluramine to maintain self-injection behavior is attributable to its meta-trifluoromethyl group. The results obtained with the present series of phenylethylamines extends these findings and suggests that ring substitutions in general may decrease the potency of the phenylethylamines in maintaining self-injection behavior. The seven

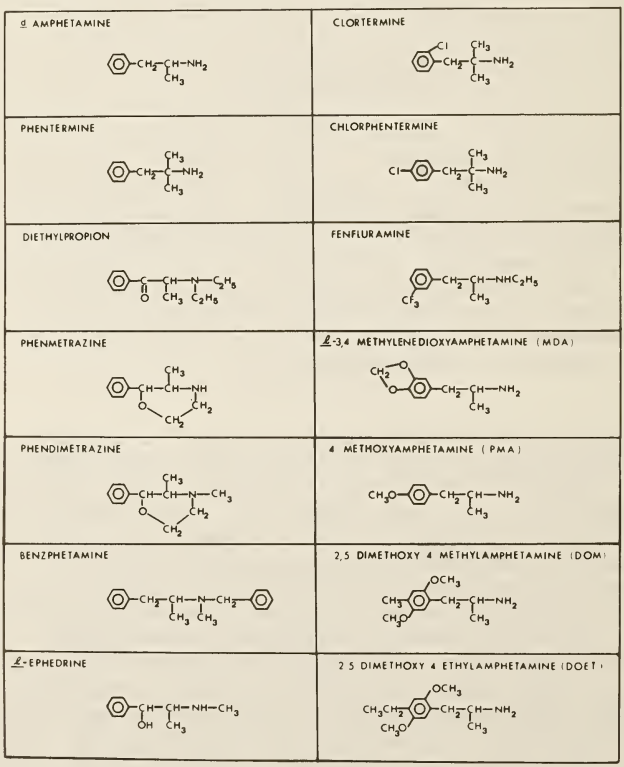

Figure 3. Chemical structures of the 14 phenylethylamines tested to determine whether they maintained drug self-administration.

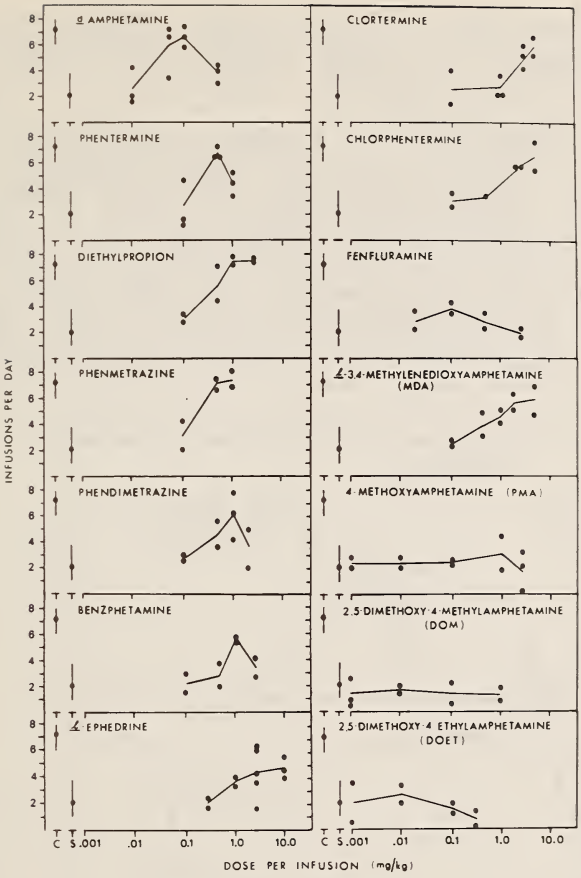

Figure 4. Average number of injections per day with 14 phenylethylamines. Intravenous injections were delivered upon completion of 160 lever presses: a 3-hr timeout followed each injection permitting a maximum of eight injections per day. C indicates mean of all the 3-day periods with cocaine which immediately preceded every substitution of a phenylethylamine or saline. S indicates mean of day 8-12 after substitution of saline (two saline substitutions in each of 15 animals). Brackets indicate ranges of individual animal's means. Drug data points indicate mean of days 8-12 after substitution of a drug for individual animals. Lines connect means at indicated doses of drug.

compounds shown in the right columns of Figures 3 and 4 had substitutions on the phenyl ring, and these compounds were generally less potent (on a mg/kg basis) in maintaining self-injection than the compounds in the left columns of Figures 3 and 4 which did not have ring substitutions.

Figures 5, 6 and 7 present additional results from testing a range of other CNS stimulants (i.e., cocaine, caffeine, and nicotine) and CNS depressants (i.e., various barbiturates and benzodiazepines) using the substitution procedure.

The reinforcing efficacy of a series of CNS stimulant drugs was systematically evaluated using the progressive-ratio procedure described above. Figure 8 shows the results of the progressive-ratio breaking point determinations over a range of doses with fenfluramine, chlorphentermine, diethylpropion, and cocaine. Doses of fenfluramine (0.02, 0.1, 0.5 and 2.5 mg/kg) did not maintain criterion self-injection performance in the two baboons tested, and therefore were assigned breaking point scores of zero. As shown in Figure 8, chlorphentermine maintained self-injection performance at

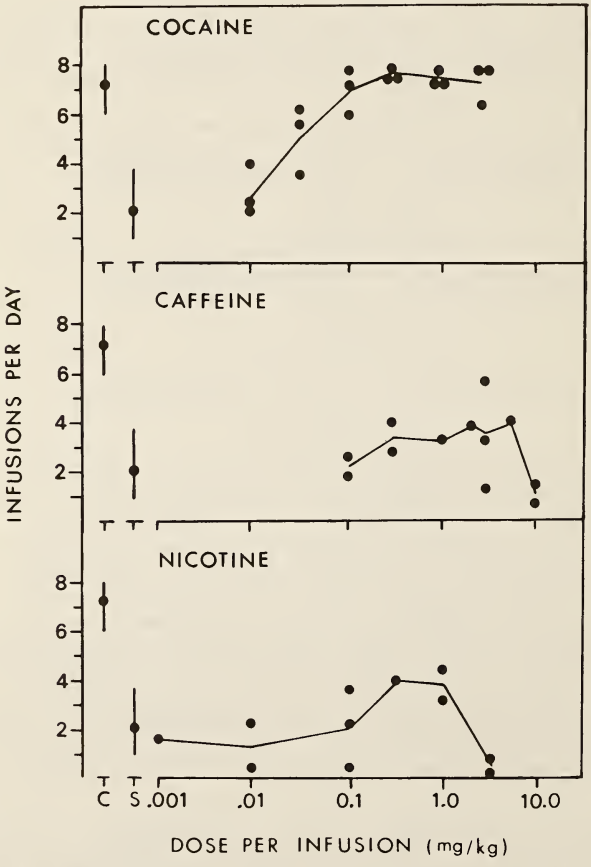

Figure 5. Average number of injections per day as a function of dose of cocaine, caffeine, and nicotine. Details of the experiments are presented in the legend for Figure 4.

some of the intermediate doses tested (1.0, 3.0, 5.6 mg/kg) in three baboons. In all three animals, lower and higher doses failed to maintain criterion self-injection performance. In the fourth baboon tested (SA), chlorphentermine did not maintain self-injection performance at the doses tested (1.0, 3.0 5.6 mg/kg). As shown in Figure 8, 0.1 mg/kg diethylpropion did not maintain self-injection performance, while at higher doses ranging between 1.0 and 10.0 mg/kg, the drug maintained behavior in all five baboons tested. Therefore, the dose-breaking point function with diethylpropion was an inverted U-shaped curve with a peak at 1.0 or 3.0 mg/kg. And finally, Figure 8 shows that the 0.01 mg/kg cocaine dose did not maintain performance; the 0.03 mg/kg dose maintained performance in three of the four baboons tested; and doses of 0.1, 0.4 and 1.0 mg/kg maintained self-injection behavior in all five baboons. Examination of the figure reveals that for the four baboons which were exposed to a number of intermediate doses of cocaine, the breaking point values generally increased with increases in dose up to 0.1 or 0.4 mg/kg.

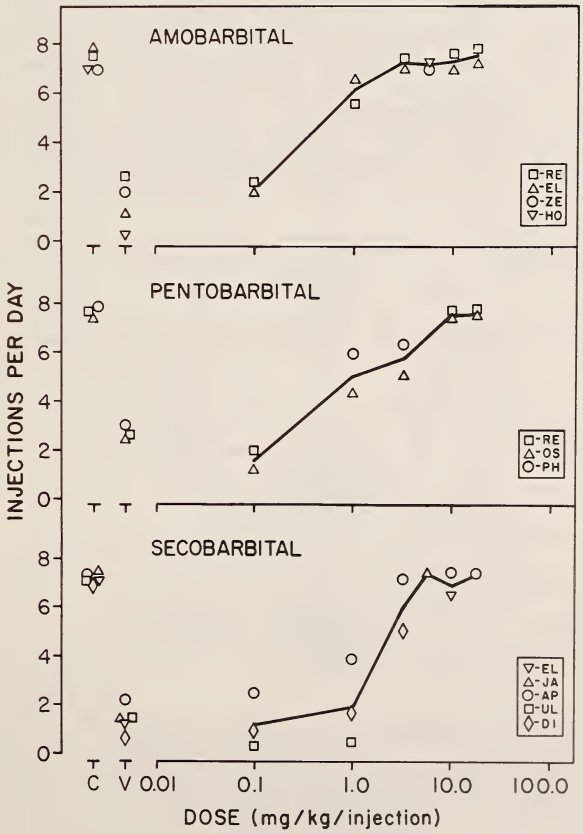

Figure 6. Average number of injections per day as a function of dose of three barbiturates. Details of the experiment are presented in the legend for Figure 4.

Within-animal comparison of the maximum breaking points maintained by the different drugs indicates that cocaine generally maintained the highest breaking points, followed in order by diethylpropion, chlorphentermine, and fenfluramine. More specifically, within-animal comparisons of the data presented in Figure 8 show that there were doses of cocaine which maintained higher average breaking points than all the doses of diethylpropion, chlorphentermine and fenfluramine tested. Similarly within-animal comparison reveals that there were doses of diethylpropion which maintained higher breaking points than all doses of chlorphentermine and fenfluramine, and finally that there were doses of chlorphentermine which maintained higher breaking points than all doses of fenfluramine.

Utilizing information collected during the initial screening of drugs, it has been possible to develop another potentially valuable dimension for ranking the abuse liability of anorectic drugs. The rationale for the dimension is similar to that for the Therapeutic Index, which provides a measure of the toxicity of a drug in terms of a ratio expressing the relationship between the therapeutic or effective dose and a dose which produces a given toxic effect. In the present case, the Anorectic-Reinforcement Ratio provides a dimension for rank ordering drugs in terms of a ratio between two doses: a dose which produces a specified anorectic effect ("therapeutic" effect), and a dose which produces a specified reinforcing effect ("toxic" effect). Clearly, the most desirable

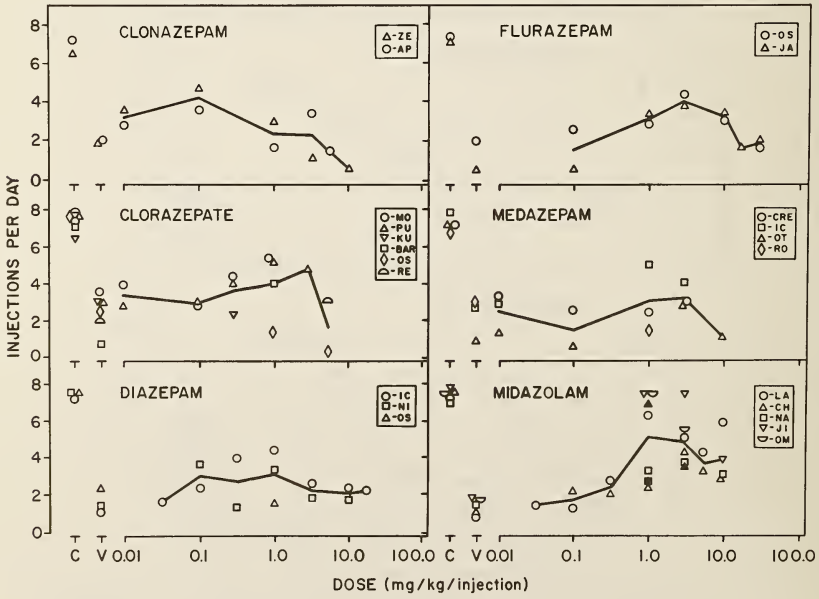

Figure 7. Average number of injections per day as a function of dose of six benzodiazepines. Details of the experiment are presented in the legend for Figure 4.

anorectic drug would have potent anorectic properties but minimal reinforcing properties. An undesirable anorectic drug would be a weak anorectic but a powerful reinforcer. Undoubtedly, existing anorectic drugs fall on a continuum between these extremes; a quantitative measure of this continuum is provided by the Anorectic-Reinforcement Ratio, and a number of substituted phenylethylamines and cocaine were evaluated using this measure.

The analysis of the reinforcing properties of a drug required examination of a substantial range of doses. Therefore, for many of the drugs analyzed, the lowest reinforcing dose (dose which maintains

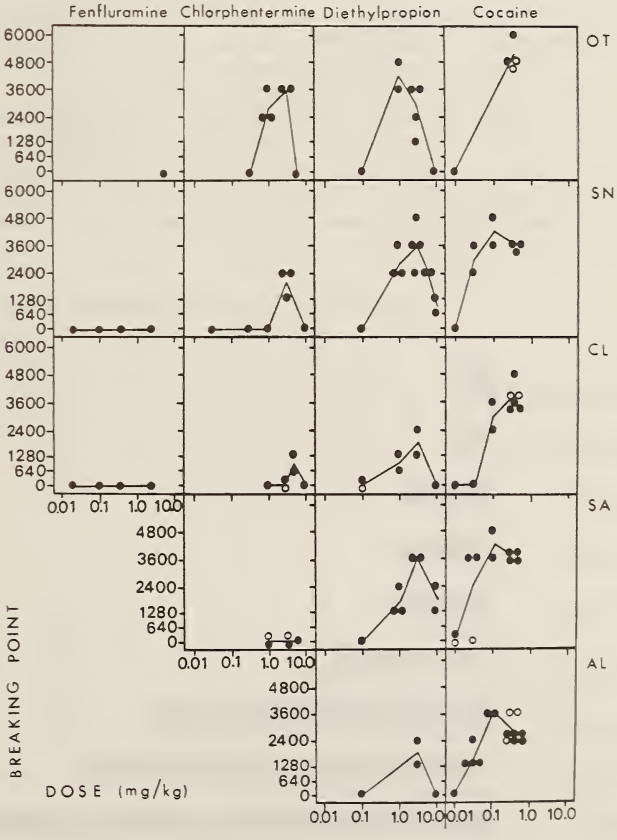

Figure 8. Breaking point values for doses of fenfluramine, chlorphentermine, diethylpropion, and cocaine in five baboons. Ordinates: breaking points; Abscissae: Dose (mg/kg/inj.). Each point represents a single breaking point observation. Lines connect the means of the breaking point observations at different doses of drug. Filled circles indicate data obtained during the first exposure to a drug dose. Unfilled circles indicate data obtained during a second exposure to a drug dose.

self-injection performance at FR 160) had already been determined. This dose provided the denominator of the Anorectic-Reinforcement Ratio (Table 1, Column B). And in the course of evaluating the reinforcing properties of the drugs under study, concurrent assessments were made of the effects of these compounds on food intake. Increasing doses of all drugs were associated with decreases in the total number of food pellets taken each day. The dose which suppressed food intake to 50 percent of saline control levels was calculated individually for all compounds on the basis of a regression line fitted to the raw data and these values are shown in Table 1, Column C for each of the indicated drugs.

Column D, Table 1 and the filled bars of Figure 9 show the resulting Anorectic-Reinforcement Ratios (based upon adjustment to an arbitrarily assigned d-amphetamine value of 1.0) derived from the relationship between food suppression dose (i.e., Column C, numerator) and criterion reinforcing dose (i.e., Column B, denominator) for each of the drugs studied. The ratio values range from a low of zero for fenfluramine and phenylpropanolamine to a high of 14.81 for cocaine, and reflect the fact that compounds with high ratio values are more potent reinforcers (relative to their anorectic potency) than compounds with lower ratio values. But the measure of

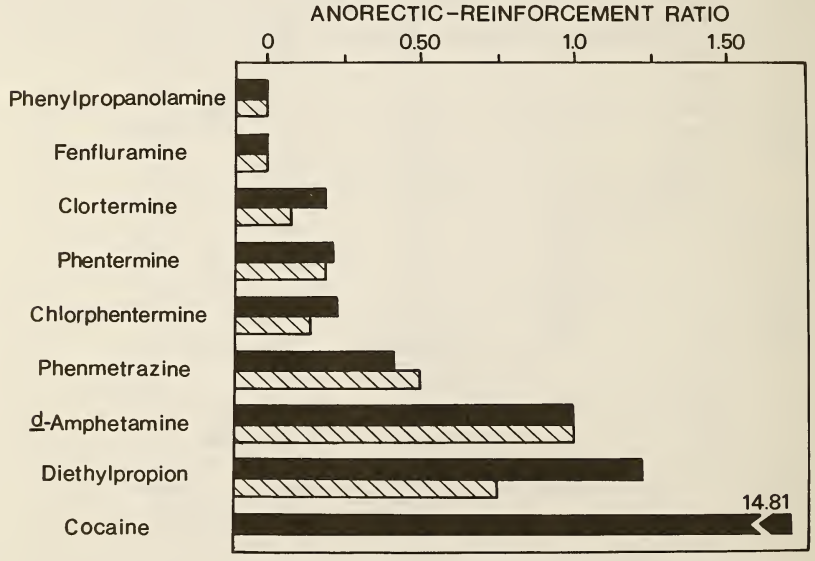

Figure 9. Anorectic-Reinforcement Ratios for cocaine and eight anorectic drugs. Filled bars show data derived entirely from baboon experiments. Striped bars show data derived from both human clinical information and baboon experiments. Compounds with high ratio values are more potent reinforcers (relative to their anorectic potency) than compounds with lower ratio values.

Table 1. Anorectic-Reinforcement Ratio - Fourteen anorectic drugs and cocaine. All doses are expressed on the basis of the hydrochloride salts except for d-amphetamine and l-amphetamine which are expressed as the sulfates, and phendimetrazine which is the tartrate. To facilitate comparison, ratios were adjusted to an arbitrarily assigned d-amphetamine value of 1.0. Numbers in parentheses indicate the number of observations on which the reinforcing dose and food suppression dose are based.

A	B	C	D	E	F
Drug	Lowest Reinforcing Dose in Baboon (mg/kg/infusion)	Dose Suppressing Baboon Food Intake 50% (mg/kg/day)	Ratio C / B	Lowest Recommended Human Anorectic Dose (mg/day)	Ratio E / B
Cocaine	0.03 (40)	16.0 (26)	14.81	--.-	-.--
Diethylpropion	0.5 (14)	22.0 (14)	1.22	75	0.75
d-Amphetamine	0.05 (13)	1.8 (10)	1.0	10	1.0
Phendimetrazine	1.0 (9)	15.9 (9)	0.44	70	0.35
Phenmetrazine	0.5 (7)	7.4 (7)	0.41	50	0.50
d-Methylamphetamine	0.1 (7)	0.98 (10)	0.27	7.5	.375
Chlorphentermine	2.5 (8)	20.3 (8)	0.23	77.9	0.16
Phentermine	0.5 (9)	3.7 (9)	0.21	18.7	0.19
Benzphetamine	0.5[1] (8)	3.5 (8)	0.19	25	0.25
Clortermine	3.0 (10)	21.0 (10)	0.19	50	0.08
Mazindol	0.3 (5)	1.6 (5)	0.15	4	0.07
l-Amphetamine	1.0 (9)	3.9 (9)	0.11	--	--
l-Methylamphetamine	3.0 (12)	1.25 (12)	0.01	--	--
Fenfluramine	9 (10)	7.0 (10)	0	60	0
Phenylpropanolamine	9 (9)	48.1 (9)	0	75	0

anorectic potency as determined with the baboon could be confounded by non-specific psychopharmacological effects such a drug-induced sensory or motor decrements. To provide more information about anorectic potency of the drugs, an alternative set of values was derived by utilizing the lowest recommended daily human anorectic doses. These doses appear in Column E of Table 1, and provide the numerator for computing a comparative set of ratio values (Column F). Since cocaine is not used clinically as an anorectic, no entry appears in Column E. Comparison of the values in Columns D and F (also the striped bars vs. the filled bars of Figure 9) show the correspondence between the ratios based upon these two independent measures of anorectic potency.

Although the progressive-ratio procedure provides a useful measure of the relative reinforcing efficacy of drugs, the procedure is quite time consuming. An alternative procedure was therefore examined to determine whether it might provide a more efficient alternative to the progressive ratio procedure. Specifically, the alternative procedure involved measuring stable response rates on a drug maintained fixed-ratio schedule. A study was undertaken to determine whether fixed-ratio schedules and progressive-ratio schedules would provide similar information about the relative reinforcing efficacy of different cocaine doses. The progressive-ratio procedure was identical to that previously described. On the fixed-ratio schedule, 160 responses were required for each injection. Each injection was followed by a timeout of either 3 or 12 hours. Each dose of cocaine was examined for at least 15 days and until response rates showed no trends. Figure 10 shows that with the 3-hour timeout, the dose-breaking point function on the progressive ratio schedule (left-hand column) was similar to the dose-response rate function on the fixed-ratio schedule (center column). As shown, these dose-effect functions were inverted U-shaped curves characterized by a graded ascending limb (0.01 - 0.32 mg/kg) and a downturn at the highest dose (3.0 - 4.0 mg/kg). On the fixed-ratio schedule the downturn in the dose response rate function was attributable to a cumulative drug effect as revealed by manipulation of timeout duration, analysis of sequential interresponse time distribution, and cumulative response records. Overall the study showed that these fixed-ratio and progressive-ratio schedules provide similar information about the relative reinforcing efficacy of different cocaine doses, and that both schedules may be useful in the assessment of drug reinforcing efficacy.

2. Methods and Results with Animal Psychophysical Procedures for Evaluating the Sensory/Motor Effects of Drugs

The procedure for determining behavioral toxicity with a range of drugs has previously been described in detail (Brady, Bradford, and Hienz, 1979; Hienz and Brady, 1981; Hienz, Lukas, and Brady, 1981) and focuses upon a reaction time (RT) methodology with laboratory baboons. This procedure has already been used extensively with primates as an index of sensory function (Stebbins and Coombs, 1975). Briefly, in the RT procedure, an animal is required to press and hold down a lever for a variable time, following which a signal is presented (e.g., a light flash or tone burst). Release of the lever within 1.5 sec. following the onset of the signal is then

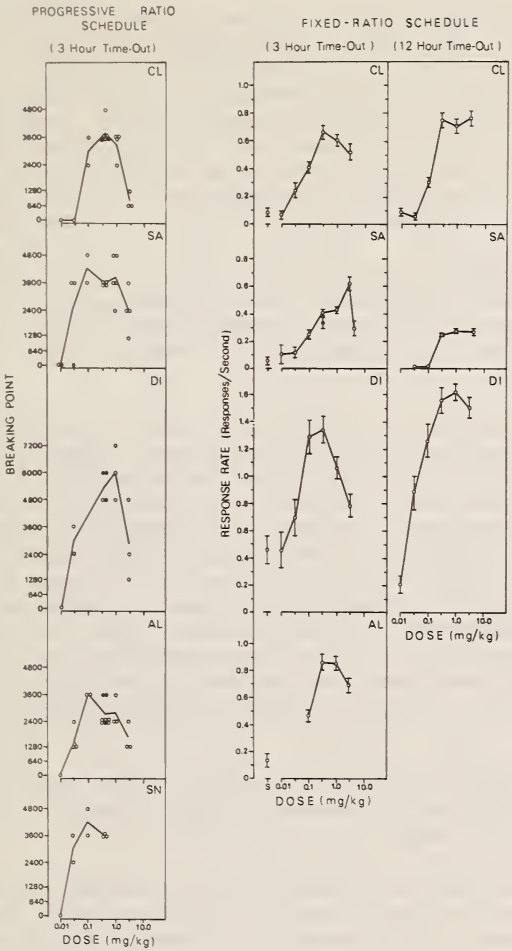

Figure 10. (Left-hand column) Breaking point values for cocaine in 5 baboons: Y-Axis = breaking point; X-Axis = cocaine dose (mg/kg/inj.), log scale. Each point represents a single breaking point observation. Lines connect means at different doses of drug. (Right-hand column) Response rates maintained by saline and various cocaine doses in 4 baboons on an FR 160 schedule with either a 3-hr or 12-hr timeout following each injection: Y-Axis = response per second; X-Axis = cocaine dose (mg/kg/inj.), log scale; S = saline. Data points and brackets indicate mean response rate ± SEM for the last 25 injections (the only exceptions are the data points for SA at 0.32 and 0.1 mg/kg with the 12-hr timeout, which are based on the last 12 injections). Unfilled circles = data obtained during first exposure to a drug dose; filled circles = data obtained during second exposure to a drug dose.

reinforced with food presentation (190 mg banana pellets). The reaction time, which is the time elapsed between the onset of the signal and the release of the lever, has been found to be inversely related to stimulus intensity, and decreases as stimulus intensity increases. This relation between reaction time and stimulus intensity is a naturally occurring one, and needs no prior training. This is a distinct advantage of using the RT procedure as a measure of sensory function. In addition, the procedure is easily employed with either auditory or visual stimuli, and can be used to obtain stimulus detection thresholds. There is also an already existing large data base on auditory reaction time with a number of primate species, including the baboon, and the procedure can be easily modified, when required, to extend research into other areas of possible drug effects (e.g., auditory frequency and intensity discrimination).

In terms of data analysis, the use of reaction time has allowed for the separation of sensory deficits from extreme motor deficits by requiring that an animal hold a lever down for a considerable period of time prior to a stimulus presentation. Thus, for example, an ataxic subject would produce a number of "premature releases" as compared to a normal subject. Further, since variability of RTs in primates is generally quite small, changes in RTs resulting from administration of specific compounds are readily detected. The measurement of the threshold levels for pure tones in primates, however, has been demonstrated not to change greatly when different reaction time criteria are used for estimating detection (Pfingst, Hienz, and Miller, 1975). Thus, a compound which produced a motor deficit resulting in longer reaction times would not necessarily cause an increase in sensory threshold estimates unless the deficit was debilitating enough to be detectable by the monitoring of premature releases. Both small and large motor effects of specific compounds can thus be separated from purely sensory effects.

The use of both auditory and visual stimuli in the reaction time procedure has provided for the assessment of drug-related changes in specific sensory systems. If drug-related changes occur in auditory RTs but not for visual RTs, for example, the observed effects can be attributed specifically to the auditory system. Further, when drug-related changes produce consistently longer reaction times to near-threshold auditory stimuli but not to high intensity auditory stimuli, a laboratory primate analogue of the clinical phenomenon which has been demonstrated to occur as a result of a brief exposure to intense sounds (temporary threshold shifts), or as a result of the use of ototoxic drugs, is provided.

Following initial shaping of lever pressing and discrimination of the holding and release components of the response, all animals were introduced to the discrete trial reaction time procedure. In the presence of a flashing cue light (5/sec), a lever press changed the flashing red light to a steady red light which remained instated as feedback as long as the animal held the lever switch in the closed position. At varying intervals (ranging 1.0 to 7.3 sec.) following initiation of this maintained holding response, a test stimulus (white light on the circular patch or tone burst through the speaker) was presented for 1.5 sec. Release of the lever within the 1.5 sec

test stimulus interval delivered a single banana pellet and initiated a 1 sec. intertrial interval (ITI) during which no stimuli were presented and lever responses re-initiated the ITI. Incorrect responses (i.e., lever presses prior to test stimulus onset or after the 1.5 sec test stimulus interval) reinstated the 1 sec. ITI without reinforcement. Following the 1 sec. ITI, the flashing red cue light signalled initiation of the next trial in the series of several hundred which comprised each daily 2 to 3 hour experimental session. Asymptotic levels of performance on this procedure typically required 2 to 3 months of such daily training sessions.

Auditory and visual thresholds were determined by randomly varying (in accordance with the method of constant stimuli) the intensity of the test stimuli from trial to trial and examining detection frequencies (i.e., correct lever releases) at each intensity. For the auditory modality (where the baboon can discriminate a range of frequencies extending to 40 kHz) four intensity levels (10 dB apart) of a 16.0 kHz pure tone were used, with the lowest level set just below the animal's estimated threshold. Interspersed among the "test" trials were a series of "catch" trials during which no tone was presented to measure the false alarm (i.e., "guessing") rate. For the visual modality, four intensity levels (0.5 log density units apart) of the white light were used with the lowest level again set just below the animal's estimated threshold. Again, "catch" trials with no light were programmed to occur intermittently. In addition, sessions involving visual threshold determinations were preceded by a 20-min dark adaptation period in the light-proof chamber followed by a 10-min "warm-up" with the various intensities of white light to be used in the session.

For both the auditory and visual threshold determinations, each test session was divided into four blocks of approximately 140 trials with each of the 4 intensity levels (plus "catch" trials) presented randomly approximately 28 times during each block. This provided 4 independent within-session estimates of the sensory thresholds and functions relating reaction time to intensity. Sensory thresholds were determined from percent correct detections at each intensity by interpolating to the intensity which produced a detection score halfway between the false alarm rate ("catch" trials) and 100%. Stable auditory thresholds were based upon determinations from 3 successive test sessions with estimates which varied by no more than 4 dB. Stable visual thresholds were based upon determinations from 3 successive test sessions with estimates which varied by no more than 0.2 log density units. In both cases, such a determination of threshold stability required a false alarm rate below 30% and no systematic change trends in the data. With regard to the response latency measure of reaction time (typically skewed due to the physiological limits on lever release time), the measure of central tendency employed for such distributions was the median, with variability reported in terms of the interquartile range.

Following stabilization of the threshold and reaction time measures, preliminary studies were undertaken to explore the validity, reliability, sensitivity, and specificity of these psychophysical methods with respect particularly to the evaluation of

drugs of abuse. All drugs were administered intramuscularly at the beginning of each experimental session, followed by a 30-minute delay (dark adaptation and warm-up) before formal threshold determinations were begun. Saline control sessions were conducted between each drug session and return-to-baseline performances were required during these intervening saline control sessions before further drug administrations were programmed.

Figure 11 shows the orderly effects of increasing doses of amobarbital sodium (i.e., 3.2, 10.0, 17.0 mg/kg, i.m.) upon reaction time as a function of white light stimulus intensity in the baboon. The latency-intensity functions were recorded 1 to 2 hours after drug administration (i.e., at the peak action time) and show the sytematic relationship between drug dose and response latency at all but the lowest (i.e., threshold) intensity level. Even at the highest intensity levels where response variability is minimal, the orderly progression of increasing latencies with increasing doses is apparent.

Figure 12 illustrates the dose-dependent effects of pentobarbital upon absolute auditory and visual thresholds, and their respective median reaction times for 2 animals. All data points are the average of at least two determinations with each animal at each dose, and represent the difference between those values at peak drug action time and the corresponding saline values during the preceding day's control session. Reaction time values are for auditory stimuli presented at approximately 25 dB above the auditory thresholds, and

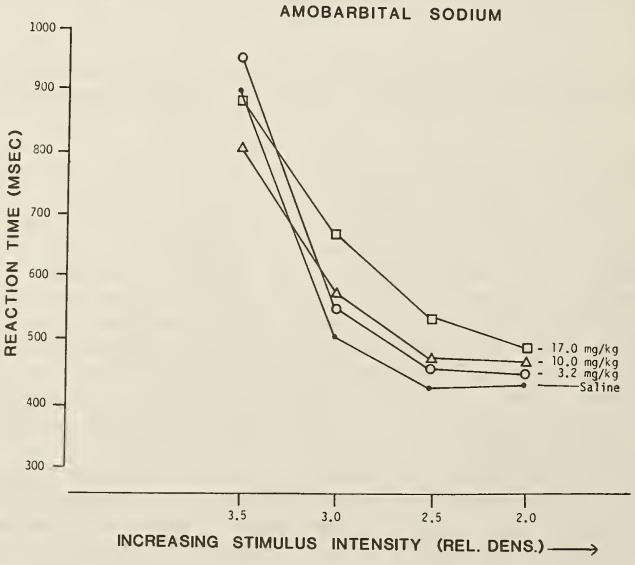

Figure 11. Reaction time change as a function of increasing visual stimulus intensity after saline or three doses of amobarbital.

for visual stimuli presented at approximately 1.25 log relative density units above the visual thresholds. The 95% confidence limits of the variability for all saline sessions preceding a drug session are shown to the left in each graph for each animal. Consistent elevations in the visual threshold and in both visual and auditory reaction times were observed following doses of 10.0 and 17.0 mg/kg with no change in auditory threshold over this same dose range.

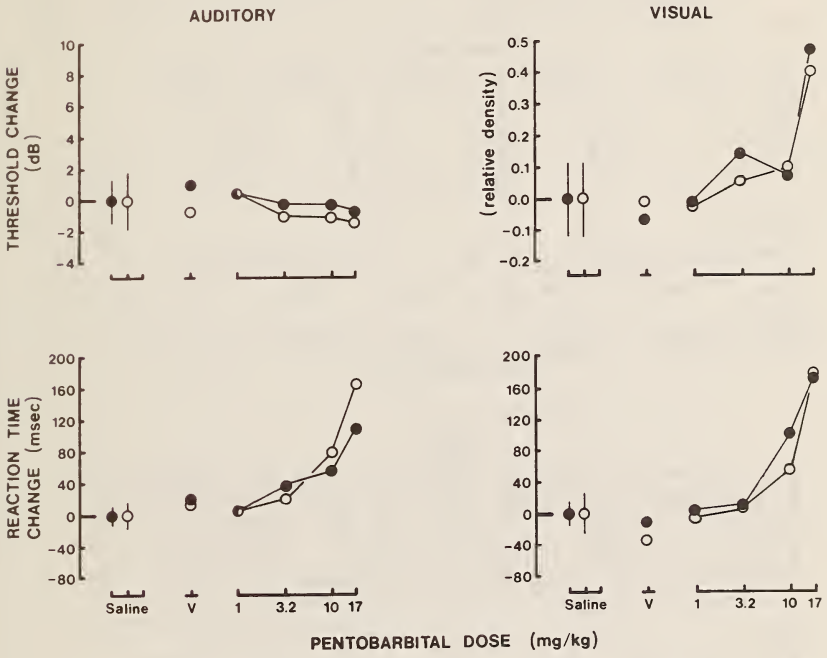

Figure 12. Changes in absolute auditory and visual thresholds and their respective median reaction times for two animals (IK = ●, PE = ○) as a function of pentobarbital dose. The 95% confidence limits in variability for all saline sessions preceding a drug session are shown to the left in each graph for each animal. Values obtained following vehicle administration are marked "V".

Figure 13 shows samples of individual auditory and visual psychometric functions and their corresponding reaction time functions during the peak time of effect for animal IK after pentobarbital administration over the dose range 1.0 to 17.0 mg/kg. Percent correct lever releases and reaction times for correct releases are plotted as a function of stimulus intensity in dB sound pressure level (SPL) for the auditory functions (top) and in log relative density units for the visual functions (bottom). The saline points were similarly derived from the control sessions conducted on days preceding each drug session. At the highest dose (17.0 mg/kg),

pentobarbital produced different effects upon auditory and visual thresholds, though similar increases occurred in both auditory and visual reaction times. The clear shift in the visual threshold function shown in Figure 13 (bottom) at 17.0 mg/kg pentobarbital occurred in the absence of any change in the auditory threshold function (Figure 13, top) under identical drug conditions. Also, the drug-induced reaction time increases were approximately parallel shifts for both the auditory and visual curves.

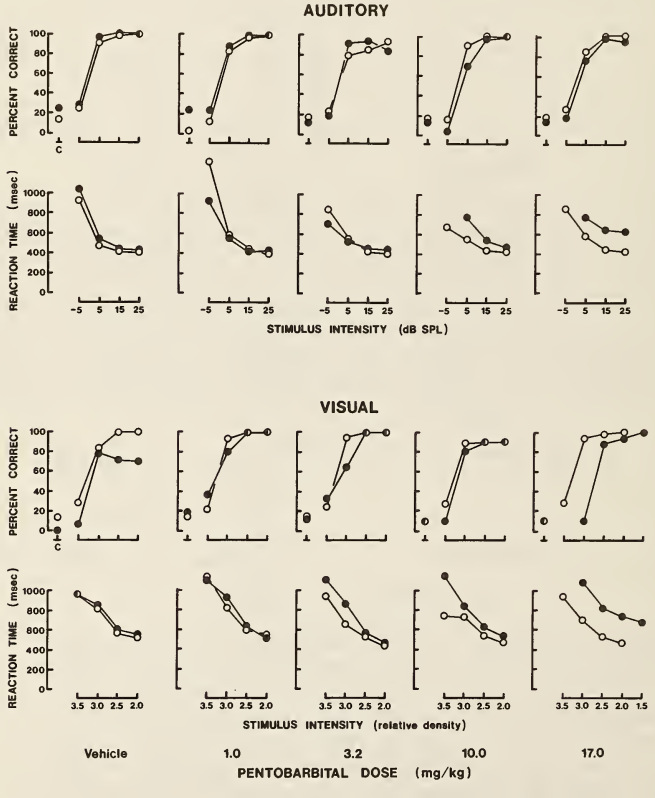

Figure 13. Changes in individual auditory and visual psychometric functions and their corresponding reaction time functions during the peak time of drug effect for animal IK over the dose range of 1.0 to 17.0 mg/kg pentobarbital. Filled circles represent data from drug sessions; open circles represent data similarly derived from the preceding day's saline control session.

Figure 14 illustrates the effects of diazepam as a function of dose (0.1, 0.32, 1.0, 3.2, 10.0 mg/kg) upon response latencies and sensory thresholds in three baboons under the same stimulus conditions and "peak drug action time" (i.e., 1-2 hours following

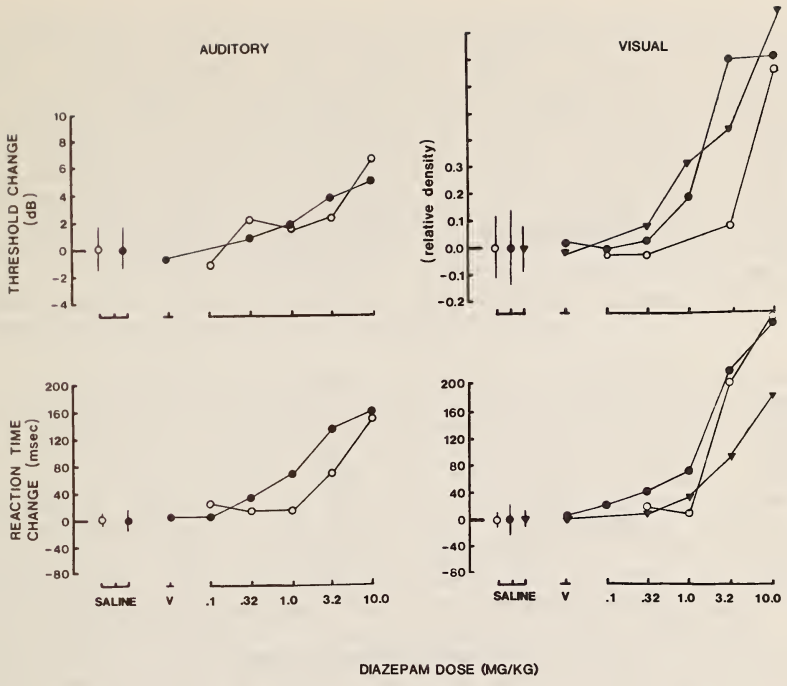

Figure 14. Changes in absolute auditory and visual thresholds and their respective median reaction times for three animals (PE = O, IK = ●, OL = ▲), as a function of diazepam dose. The 95% confidence limits for all saline sessions are shown to the left in each graph for each animal. Values obtained following vehicle administration are marked "V".

i.m. administration) relationships used with pentobarbital. The range of saline control values is shown by the vertical lines on each point. Clear effects upon reaction time and the visual threshold were observed as a function of dose, and auditory thresholds were similarly affected. For the most part, all three effects - increased response latency, visual threshold elevations, and auditory threshold increases - appeared in a dose-dependent manner with progressively greater decrements through the range from 1.0 to 10.0 mg/kg. In contrast, observations with chlordiazepoxide over approximately the same dose range (1.0 to 32.0 mg/kg) used in the pentobarbital (Figure 12) and diazepam (Figure 14) experiments, revealed only modest elevations in auditory threshold and reaction times at the highest dose (32.0 mg/kg) and no effect on visual threshold at any of the indicted doses.

Figure 15 illustrates the dose-dependent effects of d-methylamphetamine upon changes in auditory and visual thresholds, and their respective median reacton times. Consistent elevations in visual threshold were observed only at the highest doses.

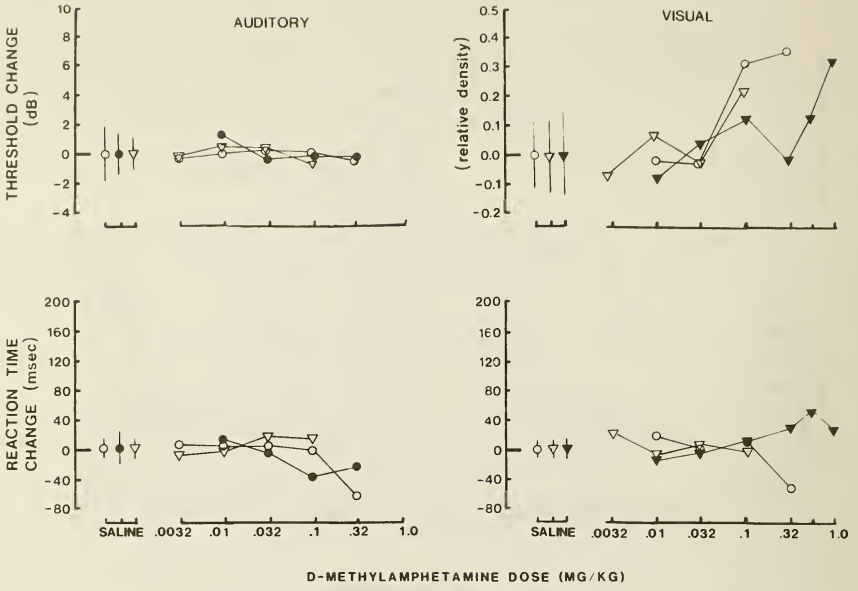

Figure 15. Changes in absolute auditory and visual thresholds and their respective median reaction times for three animals as a function of d-methylamphetamine dose. Other details are presented in the legend for Figure 12.

Significantly, these elevated visual thresholds occurred in the presence of a slight decrease in visual reaction time with one animal. Dose-related decreases in auditory reaction times were also observed with some animals during auditory testing, though auditory thresholds were unaffected over the dose range 0.1 to 0.32 mg/kg d-methylamphetamine. The effects of phencyclidine (PCP) over a range of doses (0.0032, 0.01, 0.032, and 0.1 mg/kg) upon the auditory and visual thresholds and their respective median reaction times were also studied. Although frequent disruptions in performance occurred at the highest dose, the auditory threshold and reaction time were only minimally affected throughout this dose range. Visual thresholds and reaction time were both significantly elevated at the 0.032 mg/kg dose level, however, though again frequent disruptions in performance occurred at the highest dose (0.1 mg/kg).

3. Relationship Between Reinforcing Properties and Behavioral Toxicity of Abused Drugs

The results obtained from an analysis of the relationship between the measures of reinforcing efficacy (i.e., drug self-administration) and behavioral toxicity (i.e., sensory/motor decrements) with three barbiturates (amobarbital, secobarbital, and

pentobarbital) and two dissociative anesthetics (phencyclidine and ketamine) have been detailed in a report incorporated in the present volume (Brady, Lukas, and Hienz, 1982). All five compounds maintained drug self-administration rates as a function of dose level and the dose of each compound which maintained criterion intravenous self-injection was determined. Dose-dependent increases in reaction time were also observed with all five drugs, and the dose of each compound which produced a 10% change in this measure was determined. The resulting Reinforcement/Reaction-Time-Toxicity Ratios derived from the relationship between the criterion reinforcing dose and the reaction time toxicity dose were determined for each of the five drugs studied, the ratio values ranging from a low of 0.07 for amobarbital to a high of 1.22 for phencyclidine.

Dose-dependent increases in sensory thresholds were also observed with all five drugs, and the criterion dose of each compound which produced a 50% change in either auditory or visual threshold was determined. The resulting Reinforcement/Sensory-Threshold-Toxicity Ratios derived from the relationship between criterion reinforcing dose and the sensory threshold toxicity dose were developed for each of the five drugs studied, the ratio values ranging from a low of 0.04 for amobarbital to a high of 2.0 for phencyclidine. The relationship between the criterion sensory and motor change doses and the criterion self-administration dose for the five compounds thus far studied revealed that with all three barbiturates, the doses which produced disruptive sensory/motor changes were generally higher than the doses required to maintain self-administration of these compounds. Moreover, there was a consistent relationship between the sensory and motor effects of these three barbiturates, with the reaction time effects appearing at lower doses than the sensory effects. In contrast, both ketamine and phencyclidine were differentiated from the three barbiturates by the appearance of sensory changes at doses below those which produced reaction time effects. The phencyclidine values also showed that the doses required to maintain self-administration were generally higher than the doses which produce disruptive sensory/motor changes.

The ordering of compounds derived from analyzing the relationship between reinforcing efficacy and behavioral toxicity shows that there are wide ranging differences between drugs of abuse, with the Reinforcement/Toxicity Ratios for phencyclidine being up to 10 times greater than those for amobarbital. The high ratio values reflect the fact that such compounds have disruptive sensory/motor effects at lower doses (relative to their reinforcing potency) than compounds with lower ratios. And in the case of phencyclidine, these behaviorally toxic effects can occur below the reinforcing dose. In contrast, the low ratio values reflect the fact that a drug has disruptive sensory/motor effects at higher doses (relative to its reinforcing dose) than compounds with higher ratios. Amobarbital, for example, maintained self-administration at doses below those which produce behaviorally toxic effects.

The sensory toxicity dose values for the compounds included in the present analysis were determined on the basis of criterion changes in either auditory or visual thresholds as a first approximation in analyzing their relationships to reinforcing

potency. That these compounds can produce differential effects as a function of sensory modality and drug dose, however, is illustrated in Figures 12 and 13, and has as well been documented in recent studies of the psychophysical profiles of drugs of abuse (Hienz and Brady, 1981; Hienz, Lukas, and Brady, 1981). The results of these experiments have shown, for example, that the barbiturates can produce significant elevations in the visual threshold at doses which produce no change in the auditory threshold. These findings suggest that the relationships described in the present report can be extended to provide a much more specific analysis of the nature and degree of disruptive effects under various conditions of drug self-administrtion.

Extending behavioral models for drug elevation to include analysis of the relationship between a drug's reinforcing effects and the effects of that compound from a behavioral toxicity perspective adds a critical dimension to the assessment of pharmacological activity and abuse liability.

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Development of Clinical Procedures for Abuse Liability Assessment:

Progress Report From the Behavioral Pharmacology Research Unit of the Johns Hopkins University School of Medicine and Baltimore City Hospitals

George E. Bigelow, Roland R. Griffiths, Maxine L. Stitzer, and Ira A. Liebson

For the past 15 years the Behavioral Pharmacology Research Unit laboratory at Baltimore City Hospitals has been conducting a variety of studies concerning the self-administration and effects of drugs of abuse in human volunteers. The purpose of the present progress report is to summarize work conducted during the last two years with supplemental grant support from The Committee on Problems of Drug Dependence.

In mid-1980 the Committee initiated a program to provide research grant support to clinical research laboratories for the development of clinical testing procedures to be used in the assessment of drug abuse liability in humans. A major impetus for this research grant program was the fact that the clinical laboratories of the National Institute on Drug Abuse Addiction Research Center in Lexington, Kentucky, had been disallowed, since 1976, from conducting clinical studies with volunteer federal prisoners. Prior to that time, the NIDA-ARC research program, conducted with incarcerated former drug abusers at the Lexington prison facility, had provided the major resource in this country for the clinical testing of drug abuse liability. With the closing of the Lexington clinical facility and the subsequent transfer and reopening of the ARC program in Baltimore in 1980 it was clear that there would be major changes in the nature and magnitude of the facilities available for the clinical assessment of drug abuse liability. For example, the transfer of the Addiction Research Center to Baltimore was accompanied by a dramatic reduction in the size of its clinical resources -- from approximately 60 beds, to approximately 10 beds. Also, with the loss of access to federal prisoners as research volunteers it was clear that new clinical resources and procedures needed to be developed for the conduct of clinical abuse liability evaluations.

Several questions arose: 1) What clinical settings would be appropriate for these studies? 2) What subject populations could

sensitively and appropriately differentiate compounds along the dimension of abuse liability? 3) To what extent would there be generality and transfer of the methods developed in the ARC prison facility to other settings and subject populations? and 4) What alternative procedures might be feasible and/or necessary to maximize the data yield from these new research contexts?

Since the purpose of our CPDD support was to promote procedural development, this progress will provide primarily a descriptive overview of our clinical abuse liability assessment resources and procedures, with only brief illustrative results from individual procedures.

Approach

In designing our clinical research program we have considered and attempted to assess four aspects of abuse liability: 1) The extent of maintenance of drug self-administration behavior; 2) The profile of acute subjective and physiological effects; 3) Alterations produced in cognitive/psychomotor performance; and 4) Alterations produced in global clinical mood and behavior. These dimensions are intended to assess the two crucial aspects of abuse liability -- the likelihood of a compound's being self-administered, and the likelihood of its producing disruptive effects following its administration.

Clinical Resources

As summarized in Table 1, our laboratory has utilized both a wide variety of subject populations and a wide variety of clinical research settings for conducting abuse liability evaluations.

TABLE 1. *Resources for Clinical Drug Abuse Liability Assessment*

A. SUBJECT POPULATIONS

1. Non-dependent abusers
2. Addiction treatment patients
3. "Recreational" users
4. General community volunteers
5. Medical patients

B. RESEARCH SETTINGS

1. Residential laboratory
2. Intravenous laboratory
3. Methadone treatment clinic
4. Day-laboratory sessions
5. Weight control clinic

It is possible to recruit from the community volunteers for research participation with extensive chronic abuse histories who are not physically dependent; these individuals would presumably

be most similar to the former addicts traditionally studied by the Lexington Addiction Research Center. Patients enrolled in addiction treatment also provide convenient access to volunteers with extensive abuse histories; this population (i.e., methadone maintenance patients) can also be appropriate for studies where physiological dependence upon opiates is desirable. Another convenient and readily available population is that of "recreational" drug users; these are individuals with extensive illicit drug use experiences, for whom drugs function as reinforcers, but who are not in treatment and whose patterns of use are not so intense or destructive that one would necessarily recommend treatment. General community volunteers without significant illicit drug use histories, and medical patients who are exposed to potential drugs of abuse for therapeutic reasons both provide alternative populations in which the profile of drug effects can be readily assessed; these populations can also provide a basis for assessing whether similar abuse liability discriminations are made by nonabuser versus experienced-abuser subjects.

Measures

Table 2 illustrates the range of measures which we attempt to include in our clinical drug abuse evaluations. These include a range of behavioral, subjective and physiological variables. The

TABLE 2. *Array of Measures Used in Clinical Abuse Liability Assessments*

BEHAVIORAL	
	Drug self-administration
	Psychomotor/cognitive performance
	Observer ratings of mood and behavior
SUBJECTIVE	
	Drug liking
	Symptom ratings
	Mood ratings
	ARCI scales
PHYSIOLOGICAL	
	Vital signs
	Pupil diameter

behavioral measures include indices of drug self-administration behavior, psychomotor/cognitive performance, and observer ratings of global clinical mood and behavior. The subjective measures include evaluations of subjective drug liking, symptom rating scales, mood rating scales and various scales of the Addiction Research Center Inventory. The physiological measures include periodic vital signs assessment and, for studies of opioids, measures of pupillary diameter.

One general method which we have used to assess relative drug abuse liability involves a series of forced exposure trials to the various test doses or test compounds followed by a choice trial, in which the subject himself chooses which of the previously-experienced test conditions he will receive again. Experiments proceed as a series of alternating forced exposure trials and choice trials. The forced exposure trials permit evaluation of the profile and time-course of subjective and behavioral effects in a manner similar to that traditionally used by the NIDA Addiction Research Center. The added choice trials, however, provide an objective behavioral measure of the relative reinforcing efficacy of the test compounds.

Residential Laboratory

Within our residential laboratory we have used this alternating forced-exposure/choice-trial procedure to compare diazepam (50 - 400 mg) and pentobarbital (200 - 900 mg) in experienced sedative abusers. In that previously-reported study (Griffiths et al. 1980) the subjective liking data generally paralleled the behavioral choice data -- with both active drugs being preferred over placebo, and with higher doses of pentobarbital being preferred over lower doses, but with relatively little diazepam dose preference over the range tested. Comparisons between the two active drugs, using intermediate doses producing similar magnitudes of overall sedative effect, showed a uniform preference for pentobarbital over diazepam.

Elsewhere in these proceedings Griffiths et al. report more recent data from our residential laboratory indicating differential effects of pentobarbital and diazepam upon global clinical mood and behavior; disturbances in mood and behavior were seen following diazepam (50 - 100 mg/day) which did not occur following pentobarbital (200 - 400 mg/day).

At last year's CPDD meeting McLeod et al. (1982) presented data illustrating use of the residential laboratory for assessing the effects of pharmacological treatments upon the signs and symptoms of the opioid abstinence syndrome and upon opioid drug-seeking and self-administration behavior during methadone detoxification.

Intravenous Laboratory

One evaluation procedure developed specifically via our support from the Committee on Problems of Drug Dependence is our intravenous laboratory. In this procedure subjects participate in sessions of several hour duration 2 - 3 times per week while intensive psychophysiological and subjective data are collected to evaluate the profile and time course of effects of intravenously administered drugs. An advantage of this intravenous procedure is the speed of the drug effect onset and time course, which permits intensive multifaceted assessment of changes over a relatively brief period within a standardized laboratory setting.

At last year's CPDD meeting (McCaul et al. 1982) and also elsewhere in these proceedings, McCaul et al. have presented data describing the profile and time course of the subjective and physiological effects of a range of hydromorphone doses in experienced opioid abusers and describing the effects of methadone maintenance treatment (i.e., opioid tolerance) on those effects. These data have identified symptom ratings and overall drug "high" ratings which appear to track the time course of opioid agonist effects at least as sensitively as the subjective effect indices traditionally used in opioid evaluations by the NIDA Addiction Research Center.

Day-Laboratory

A second procedure developed specifically via our support from CPDD is our day-laboratory procedure for evaluating drugs in "recreational" users and in general nonabuser community volunteers. In these studies volunteers from the community participate in within-subject experimental designs in which they spend a number of hours in the laboratory on several different days while subjective and behavioral effect time-course data are collected concerning each of several drug or dose test conditions. In studies in this setting we have evaluated the ability of "recreational" drug users to detect the effects and time course of normal therapeutic dose levels of various benzodiazepines versus placebo, and we have assessed the effects upon psychomotor/cognitive performance of these therapeutic dose levels both when given alone and when combined with various doses of ethanol (0.75 and 1.5 ml/kg). Benzodiazepine doses have been 5 mg diazepam, 1 mg lorazepam, or 7.5 mg clorazepate, each given twice daily at a 4-hr interval; when ethanol was given it accompanied the second of the daily drug doses. Results have shown that in this subject population both subjective liking measures and psychomotor/cognitive performance measures were able sensitively to differentiate among these benzodiazepines even at these modest dosage levels and that it is possible in this setting to track the time course of these drug effects and to assess their interaction with ethanol. Detailed data analysis is still in progress.

Weight Control Clinic

A final setting in which we have conducted comparative clinical evaluations of drugs of potential abuse is a behavioral pharmacological weight control treatment research clinic (Bigelow et al. 1980). Here it is possible to evaluate the effects and self-administration of drugs among nonabuser volunteer patients who are exposed to the test drugs for therapeutic reasons. We have been using this setting for comparative evaluations of the various phenylethylamine CNS stimulant-anorectics which are marketed for weight control. The general procedure is a within-subject experimental design involving cycles of forced exposures to the test compounds followed by choice trials, as described earlier. Results have shown d-amphetamine (5 - 10 mg tid) to be preferred over fenfluramine (20 - 40 mg tid) and diethylpropion (75 mg con-

trolled release) to be preferred over chlorphentermine (65 mg). The behavioral choice procedure has proven its value by detecting differences between compounds which were not detected by comparing the effects of forced exposures. While it is not possible to know whether variations in drug self-administration within this therapeutic context are related to variations in the reinforcing efficacy or abuse liability characteristics of these compounds, it is interesting that the between-drug differences so far observed have all been in a direction congruent with both animal and clinical data concerning relative abuse liability.

Conclusions

We have found that a variety of settings and subject populations appear adaptable to providing orderly clinical data concerning the relative reinforcing efficacies and abuse liability of drugs. Specifically, we have found that such studies can be conducted in nonresidential settings and with volunteer participants without chronic drug abuse histories. Many of the general methods developed by the NIDA-ARC for conducting these evaluations with incarcerated postaddicts have proven adaptable to these other settings and other populations -- especially the general approach of examining the profile and time course of subjective drug effects and the use of liking measures and the Addiction Research Center Inventory as assessment instruments. In addition to the ARCI scales we have found that there are a variety of other self-report measures which appear to provide sensitive indices of relative drug effects -- at times even more sensitively than the ARCI scales. Finally, we would emphasize the value of the behavioral measures in these procedures. Behavioral choice measures of drug preference would appear to provide us with the most straightforward and direct measure of the criterion we are trying to predict in abuse liability testing -- the relative efficacy of compounds in sustaining self-administration. In addition, behavioral measures of drug effects on skill performances and on global clinical behavior provide useful complementary data concerning the relative risks which might ensue consequent to the use or abuse of these compounds.

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Comparative Assessment of Potential Abuse Liability of Natural and Synthetic Cannabis Compounds

Jack H. Mendelson, Nancy K. Mello, Barbara Lex, Jon Pehrson, and Samuel Bavli

INTRODUCTION

Laboratory and clinical investigations have indicated that cannabis compounds may have therapeutic applications as analgesics, antiemetics, bronchodilators, antihypertensives and in the treatment of glaucoma (Babor et al. 1975; Cohen and Stillman 1976). Since cannabis compounds produce hypnosedative and psychoactive effects in humans and are commonly used as recreational drugs, the risk of illicit diversion may increase as cannabis is used more widely in medicine. The situation is analogous to the problems associated with the development of new analgesics. The rationale for FDA scheduling of prescription opioid drugs is to reduce drug dependence liability through illicit distribution. During 1979, the Committee on Problems of Drug Dependence, Inc. initiated a program to develop methodologies to assess the abuse dependence liability of non-opioid drugs which may have applications in clinical medicine. This report describes a new behavioral paradigm for the evaluation of potential abuse liability of a synthetic cannabis compound in man.

Following anecdotal reports that marijuana smoking reduced nausea and vomiting associated with cancer chemotherapy, more systematic observations suggested that naturally occurring Δ^9 tetrahydrocannabinol was an effective antiemetic agent for patients receiving chemotherapy (Herman et al. 1977). The active compound in marijuana Δ^9 THC is delivered in unpredictable doses of varying potency in marijuana cigarettes. Consequently, synthetic cannabis derivatives were prepared for use as adjunctive agents in cancer chemotherapy. Nabilone is a modified cannabinol derivative which has been shown to be efficacious in suppressing severe nausea and vomiting induced by cancer chemotherapy (Isbell et al. 1967). Studies of the clinical pharmacology of Nabilone have been carried out with normal healthy male volunteers and acute administration of 1 and 2.5 mg doses produced relaxation and sedative effects (Lemberger and Rowe 1975). A minimal degree of euphoria, dry mouth, tachycardia and postural hypotension were observed after 1 and 2.5 mg dosage (Lemberger and Rowe 1975). Although euphoria

achieved statistically significant levels, the biological significance of these observations is questionable since the increment in pulse rates were relatively small.

Operant Contingent Drug Choice: Eighteen subjects (7 regular users, 6 intermittent users, and 5 casual users), worked to obtain an active marijuana cigarette. Two subjects (1 regular and 1 intermittent user) worked to obtain 17.5 mg of oral THC. None of the subjects worked for Nabilone and three subjects (all occasional users) elected not to work for any drug on the fifth study day. All twenty-three subjects worked to obtain the $10.00 monetary reinforcement on the fifth study day and all earned the requisite 3600 reinforcement points within 30 to 40 minutes. There were no significant differences in the time spent at operant work or the efficiency of operant performance for money reinforcement between the regular, intermittent and occasional users. There were no significant differences in operant performance for monetary reinforcement between those subjects who had elected to smoke marijuana, ingested THC or who had not worked for any drug prior to the opportunity to earn operant points for money.

DISCUSSION

The major findings obtained in this study were: subjects accurately discriminated marijuana cigarettes, orally administered THC and Nabilone from their placebos; marijuana smoking produced the greatest change in subjective responses for the "high" and "stoned" rating scales; marijuana was the drug of choice for 90 percent of the subjects (20 of 22) who elected to work at an operant task for drug acquisition. Taken together these data strongly suggest that marijuana smoking is the preferred mode of cannabis self-administration by regular, intermittent and occasional marijuana users and that orally administered THC compounds are much less preferred (only two subjects who worked for a drug of choice selected oral THC). Since no subject elected to work for Nabilone and since Nabilone produced significantly less change in self-rating scores than marijuana, we conclude that Nabilone would have relatively low abuse potential liability for individuals who have a wide spectrum of past history of marijuana use.

This study also demonstrated that evaluation of new pharmacotherapies (with psychoactive properties) for safety and efficacy may also be supplemented with procedures to determine potential abuse liability in humans. The research design and procedures utilized in this study may provide a useful model for assessing the reinforcing properties and potential abuse liability of psychoactive drugs for selected populations who may be at risk for drug abuse.

or was unable to attend to work or school activities during the five study days. All subjects were drug free during the study. Daily urine drug screens did not reveal any psychoactive substances such as opiates, sedative hypnotics, stimulants, tranquilizers or depressants for any subject.

Subjective Levels of Intoxication: The subjects were able to discriminate placebo from active drugs with 98 percent accuracy. Following marijuana smoking, all subjects reported "high" scale scores which were significantly greater ($p < .01$) than after placebo administration. Subjects in the regular, intermittent and occasional groups did not differ significantly in "high" ratings following marijuana smoking. However, heavy and intermittent users reported significantly lower "high" scores after THC than after marijuana smoking ($p < .05$). Occasional users reported equivalent "high" scores after marijuana smoking and oral THC administration. Following Nabilone administration all subjects' reports of "high" were significantly lower than after marijuana smoking ($p < .05$). The degree of "high" following oral THC administration and Nabilone did not differ significantly for any group. Thus in terms of perceived high, the rank order from most to least was smoked marijuana >oral THC >Nabilone >placebo.

Following marijuana smoking, a statistically significant increment in "stoned" scores was obtained for all three subject groups ($p < .05$) and there were no statistically significant differences between these groups. Following THC and Nabilone administration, "stoned" scores were significantly lower than after marijuana smoking for all three subject groups ($p < .05$). There were no statistically significant differences in "stoned" scores between THC and Nabilone administration for the three subject groups.

Changes in Mood States: Following placebo administration no statistically significant differences occurred for any of the subject groups in POMS elation factor scores. After marijuana smoking, a small but statistically significant increment in elation scores ($p < .05$) was reported by the regular users. No significant changes in the POMS elation factor scores were observed for any of the subject groups following THC or Nabilone administration. However, there was a small but consistent decrement in the POMS elation factor score at the end of each experimental session for each subject group. The most parsimonious explanation for this observation was that subjects tended to become more fatigued toward the end of each experimental day assessment period.

Changes in Pulse Rate: No significant changes in pulse rate were observed for any subject group following placebo administration. Pulse rates increased after marijuana smoking and administration of THC and Nabilone. Statistically significant increases in pulse rate were observed for the intermittent and occasional users following marijuana administration ($p < .05$) and for all subjects following THC and Nabilone administration ($p < .05$). Although pulse rate increases following marijuana, THC or Nabilone administration

Δ^9 THC (Lemberger and Rowe 1975). Studies carried out by Isbell and his associates (1967) have shown that the potency of Δ^9 THC after smoking (as determined from changes in peak pulse rate) is approximately 2.6 times that after oral ingestion. The marijuana cigarettes used in the study contained 1.83 % of Δ^9 THC in each 1 gram cigarette. However, subjects actually inhaled only 1/3 of the total pyrolyzed material in any cigarette or approximately 6.1 mg of Δ^9 THC.

Sequence of Procedures: During the first four days of the study each subject received only one dose of the active compound (marijuana, Nabilone or THC) and placebos during each drug trial. Drugs were administered according to a 4 x 4 Latin square design to control for sequence effects. Each drug trial day (the first, four consecutive days of study) was designated by a specific color code (blue, red, yellow or green). During these four days subjects remained on the research ward from 6:00 p.m. each evening until 7:00 a.m. the following morning when they were allowed to depart for their usual school or job activities.

During the first four days of drug administration, subjects provided a urine sample for drug screening examination when they reported to the laboratory. Questionnaire instruments administered to assess the type and quality of subject drug effects included a Profile of Mood States (POMS), the Adjective Check List (ADCL) and a "High" scale to assess subjects' levels of intoxication. These instruments have been successfully employed in previous studies to assess marijuana effects in humans (Mendelson et al. 1976; Orr and McKernan 1981; Rossi et al. 1978)). Subjects were also asked to provide a placebo-drug report to indicate whether they believed they had received an active drug or a placebo. Blood samples were obtained for determination of pituitary-gonadal hormones prior to and following drug administration. These data will be reported elsewhere.

On the fifth day of the study, subjects were given an operant manipulandum and told that they could work for one dose of the red, yellow, blue or green drug which they received during the four previous consecutive days. In order to obtain one additional dose of their drug of choice, subjects were instructed to press the response key on the operant manipulandum to earn 3600 reinforcement points. Acquisition of the required number of points for their drug of choice required 30 to 40 minutes of work. Following drug administration, subjects could then work at an identical operant task to earn money. They could earn $10.00 for 3600 responses or 30 to 40 minutes of sustained operant performance.

RESULTS

Drug Safety: Eight regular marijuana users, seven intermittent users and eight occasional users completed all phases of the study. No adverse physical side effects or changes in vital signs occurred during the course of the study. No subject became ill

was not significant at low dosage administration of Nabilone (1 to 2.5 mg) (Lemberger and Rowe 1975), illicit use of the drug could occur. This report describes assessment of the reinforcing properties of a single dose of Nabilone (2 mg) in comparison to Δ^9 THC (17.5 mg), a standardized marijuana cigarette containing 1.83 % Δ^9 THC, and placebo controls. Behavioral assessment of reinforcing properties by a combination of self-reports and work-contingent choice between these four substances provides an objective index of potential abuse liability.

METHODS

Subjects: Twenty-four healthy, adult, male volunteers recruited through newspaper advertisements, provided informed consent for participation in these studies. Prior to selection for the study all subjects completed a standardized drug use questionnaire and a Cornell medical index. All subjects received a complete medical examination, an electrocardiogram, and blood and urine laboratory studies.

No subject reported a history of drug use other than marijuana and none had a history of drug dependence. No subject had a history of alcohol abuse or alcohol dependence.

Subjects selected to participate in the study were divided into three groups on the basis of their reported marijuana use. Regular users were subjects who smoked 1-3 marijuana cigarettes per day and had engaged in this pattern of marijuana use for at least one year. Eight subjects with a mean age of 26.8 years (range 23-30) and a mean weight of 163.8 lbs (range 140-216 lbs.) were regular marijuana users. Intermittent users smoked 1-3 marijuana cigarettes per week and had engaged in this pattern of marijuana use for at least one year. Eight subjects with a mean age of 25.3 years (range 22-30) and a mean weight of 158.6 lbs. (range 131-181) were intermittent (weekly) marijuana users. Occasional (monthly) users smoked 1-3 marijuana cigarettes per month and had engaged in this pattern of marijuana use for at least one year. Eight marijuana users with a mean age of 24.4 years (range 22-28) and a mean weight of 164.1 lbs. (range 133-192) were occasional marijuana users. Final data are reported on 23 subjects; one subject left the study after the first experimental day because of anxiety about his interaction with the other subjects.

Drugs: Each subject served as his own control over five consecutive days during which Nabilone (2 mg), Nabilone placebo, a standardized marijuana cigarette (1 gram containing 1.83 percent THC), a standardized marijuana placebo cigarette, 17.5 mg THC P.O., and a THC placebo were administered under double blind and double dummy conditions to control for two routes of administration e.g., smoking and oral capsules.

Drug dosage for this study was selected on the basis of 2 mg of Nabilone having equal potency of 17.5 mg of orally administered

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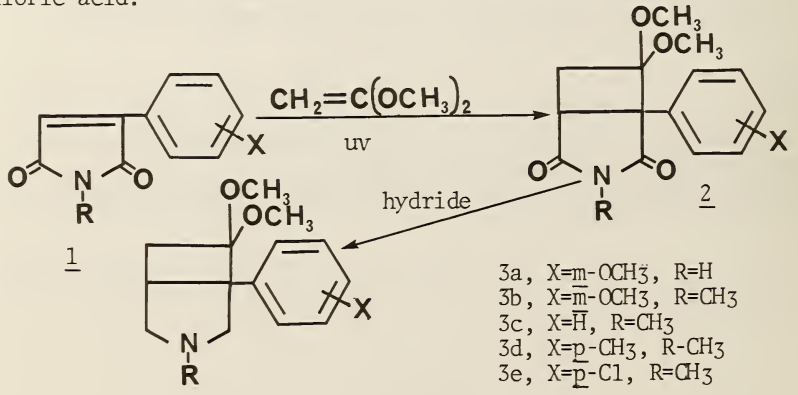
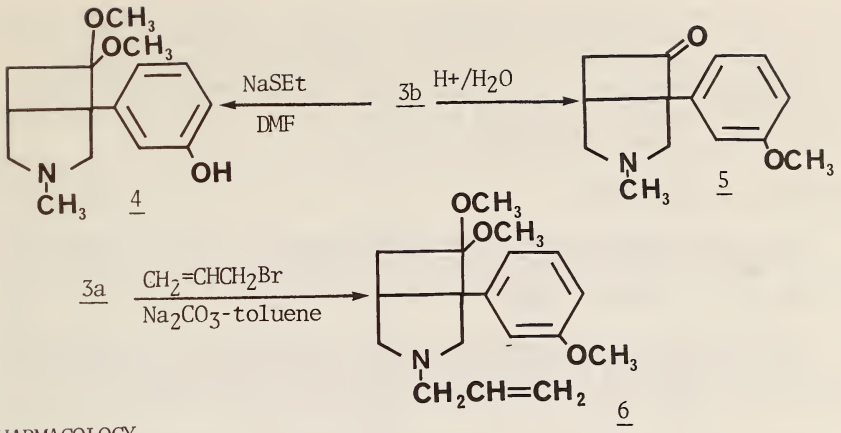
Synthesis and Analgesic Activity of 5-Aryl-3-Azabicyclo [3.2.0.] Heptan-6-One Dimethylacetals: Compounds With Extraordinary Morphine-Like Properties

J. W. Epstein, T. C. McKenzie, W. J. Fanshawe, A. C. Osterberg, B. A. Regan, L. P. Wennogle, M. S. Abel, and L. R. Meyerson

As a part of our studies of aryl azabicycloalkanes as analgesic agents (Epstein et al. 1981, 1982), we undertook the synthesis of 5-aryl-3-azabicyclo[3·2·0]heptanes (McKenzie et al. 1982). We employed a [2+2]photocycloaddition of 1,1-dimethoxyethylene to 2-phenylmaleimides, 1, [prepared by the method of Izzo (1963)]to give the cyclobutanedicarboximides 2, and subsequent reduction with sodium bis(2-methoxyethoxy)aluminum hydride gave the desired 5-aryl-3-azabicyclo[3·2.0]heptanes, 3a-3e. The structure of the photoproducts 2 was established by ^{1}H NMR spectroscopy. The bridgehead methine proton at δ 3.32 is coupled to the adjacent cis and trans cyclobutane methylene protons with a coupling constant of 4.4 and 10.5 Hz, respectively. The ring juncture was assumed to be cis. The N-methyl-m-methoxyphenyl analogue 3b was demethylated (Epstein et al.1981) with sodium ethyl mercaptide in N,N-dimethylformamide to give phenol 4. The N-allyl derivative 5 was obtained from 3a by alkylation with allyl bromide in toluene-sodium carbonate. Ketal 3b was hydrolyzed to the corresponding ketone 6 using hydrochloric acid.



3a, X=m-OCH_3, R=H
3b, X=m-OCH_3, R=CH_3
3c, X=H, R=CH_3
3d, X=p-CH_3, R-CH_3
3e, X=p-Cl, R=CH_3



PHARMACOLOGY

The results of analgesic testing using the reversal of the 3-legged gait in rats are presented in Table I, and an examination of the data suggests that these compounds fall into the category of narcotic-type compounds. The most potent members of the series are the m-methoxyphenyl 3b and m-hydroxyphenyl-N-methyl 4 congeners, while the absence of the N-methyl group in 3a significantly curtails activity. The phenyl analogue 3c retains moderate activity, while the p-chloro 3e compound is less active, and the p-methyl 3d analogue is inactive. The significant aspect of this study is that compound 3b shows considerable (ED_{50}=4 mg/kg) oral activity, and remarkable morphine-like effects (Table II). The hydrolysis product of 3b, the ketone 5, is inactive, which suggests that the ketal remains intact in vivo. The N-allyl derivative 6 is active, but the ED_{50} was not determined.

Table I also shows the inhibition of ^{3}H-naloxone binding by compounds at 25 and 0.78 micromolar. It is interesting that compound 3b shows inhibition in a range which is comparable to the less active, and inactive compounds. The phenol 4, however, shows morphine-like binding characteristics. Table III compares the IC_{50} values of 3b and 4, as well as sodium-index values. Compound 3b has an IC_{50} value around 10,000 nM with a sodium index (6.3) near that of morphine (5.1), while the phenol 4 has an IC_{50} value (61 nM) equivalent to morphine (74 nM). In addition, the sodium index of 4 (9.4) suggests that it is a pure agonist (Pert and Snyder 1973). Compounds 3b and 4 show narcotic toxicity at relatively low doses and these effects can be inhibited by naloxone. Table II summarizes these characteristics for 3b.

There are some geometric similarities between 3a and morphine that are not obvious on casual inspection. The distances and orientation from the nitrogen atom to the other three atomic features thought necessary for analgesic activity are similar to those of morphine. These salient features are a benzene ring, a quaternary carbon attached to the ring, and a hydroxyl group disposed meta

to the quaternary carbon. In addition, the two oxygen atoms of the ketal are in similar positions relative to the nitrogen as the remaining two oxygen atoms of morphine. The distance from nitrogen to the allylic hydroxyl group of morphine is 6.5Å and from nitrogen to the α-methoxyl group of 4 is 4.6Å. This is the largest discrepancy of the five features discussed.

PHARMACOLOGICAL METHODS

Inflamed Rat-Paw Reversal of Abnormal Gait. A modification (Epstein et al. 1982) of the procedure of Atkinson and Cowan (1974) was used as the primary assay.

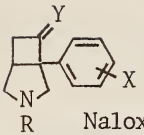
Inhibition of ^{3}H-Naloxone Binding. Inhibition of ^{3}H naloxone binding was conducted employing the procedure originally described by Pert and Snyder (1973) and modified by Ong et al. (1980).

Mouse Hot Plate Method. An adaptation of the methods of Woolfe and MacDonald (1944) and Eddy et al. (1950) was employed. Individual mice were confined on a heated surface (Techni Lab Instruments, Model 475) maintained at 55.0 ± 0.5°C and the time required to elicit a response (licking of paws or an attempt to jump from plate) was recorded. A maximum (cut-off) time of 30 seconds was used. The criterion for analgesia is a 100% increase in response time over that of vehicle treated mice.

Rat Tail Flick - Radiant Heat Method. A modification of the method of D'Amour and Smith (1941) was used. The tail of each rat was exposed to high intensity radiant heat stimulus 90 minutes after oral administration of the compound, and the time required to elicit a threshold response (characteristic tail flick) was recorded. A maximum exposure (cut-off time) of 15 seconds was employed for the high intensity stimulus. The criterion for analgesia is a 100% increase in response time over that of vehicle treated rats.

Statistics. ED_{50}'s and 95% confidence limits were calculated according to the linear arc sine transformation method of Finney (1964).

TABLE I



ANALGESIC ACTIVITY

Cpd.	X	Y	R	Naloxone Binding Conc.(μM),% Inhibition	3-Legged Gait ED_{50}(95%CL) mg/kg i.p.-rat
3a	m-OCH_3	2	H	25 0.78	>25
3b[1]	m-OCH_3	2	CH_3	25 61 0.78 7	4.0(2.8-5.6)p.o.
3c[1]	H	2	CH_3	25 62 0.78 13	<25 (4/4A)
3d[1]	p-CH_3	2	CH_3	25 62 0.78 11	R(25)
3e[1]	p-Cl	2	CH_3	25 0.78	25
4	m-OH	2	CH_3	25 99 0.78 85	3
5	m-OCH_3	2	allyl	25 69 0.78 10	<25 (4/4A)
6	m-OCH_3	3	CH_3	25 22 0.78 12	R(25)
	morphine			25 100 0.78 97	35 p.o. 0.4 s.c.

[1] fumarate [2] $(OCH_3)_2$ [3] O

Table II. Summary of Effects Induced by 3b in Mice and Rats

Procedure	Results
Reversal of abnormal gait in rats.	ED_{50} = 4.0 (2.8-5.6) mg/kg p.o.
Rat tail flick - high intensity radiant heat stimulus	ED_{50} = 5.7 (4.5-7.3) mg/kg p.o.
Mouse hot plate (55° C)	significant increase in threshold response at 20 mg/kg s.c.or p.o.
Induction of Straub tail in mice	8/8 Straub tail (12.5, 25mg/kg p.o.
Acute lethality in rats	Est. LD_{50} = 10 mg/kg i.p., 20 mg/kg p.o.
Overt Effects	
Rats	Catatonia, exophthalmus, decreased respiration, decreased motor activity (10 mg/kg i.p.)
Interactions	
Mice - naloxone (10 mg/kg i.p.)	Complete reversal of Straub tail
Rats - naloxone (25 mg/kg i.p.)	Inhibition of overt effects and lethality

Table III. IC_{50} Values in Competition Binding with ^3H-Naloxone in the Presence and Absence of Na^+ Ions

Compound	IC_{50}(nM)[a] -NaCl	+NaCl(100 mM)	Sodium Index $\frac{IC_{50}(+ Na+)}{IC_{50}(- Na^+)}$
Naloxone	46	42	1.1
Morphine	74	380	5.1
Levallorphan	9	34	3.7
3b	9,924	62,531	6.3
4	61	579	9.4

[a] IC_{50} value is defined by the concentration of drug required to inhibit by 50% the stereospecific binding of ^3H naloxone (5 nM) to homogenates of rat brain minus cerebellum in the presence or absence of 100 mM NaCl. Each value represents the mean of three separate experiments.

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Mr 2033 CL—A Novel Non-Morphine-Like Opioid Analgesic

K. Stockhaus, H. A. Ensinger, W. Gaida, H.-M. Jennewein, and H. Merz

Compounds which are acting predominantly by means of the κ receptors are different from the morphine-like μ agonists with regard to several unwanted side-effects and seem to be a new group of potent analgesics (Martin et al. 1976). In various in vitro and in vivo experiments, Mr 2033 CL was characterized as a κ agonist (Lord et al. 1977; Woods et al. 1979). The action profile of this compound has some remarkable features which will be reported here.

Drugs used: Mr 2033 CL = (±)-(1R/S, 5R/S, 9R/S, 2"S/R)-5,9-dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan hydrochloride, morphine, pentazocine, (±)-ketazocine, nalorphine, naloxone and naltrexone as hydrochlorides, Mr 2266 CL = (-)-2-(3-furylmethyl)-2'-hydroxy-5,9α-diethyl-6,7-benzomorphan hydrochloride synthezised in our laboratories, (±)-bremazocine hydrochloride (Sandoz, Basel), [^{3}H]-dihydromorphine (35.5 Ci/mmol), [^{3}H]-naloxone (50 Ci/mmol), [^{3}H]-Ethylketazocine (15 Ci/mmol) all from New England Nuclear, and [^{3}H]-D-Ala^2-D-Leu^5 enkephalin (26 Ci/mmol; Amersham).

1. Analgesia

Mr 2033 CL is a very potent analgesic drug in different test models and species (Fig. 1). After subcutaneous administration it is about 20 times more potent than morphine. Its duration of action is longer than that of pentazocine in different assays. Like ketazocine it is active in the Haffner test, the hot-plate test, and the tail-flick model in mice, while pentazocine and bremazocine are inactive in these rigorous test models.

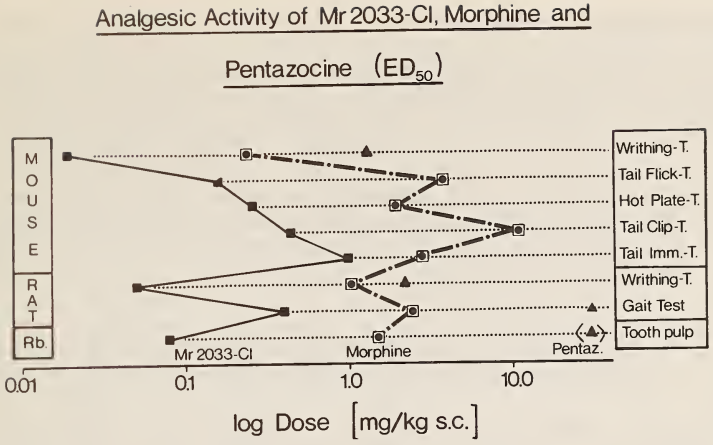

Figure 1. Analgesic activity of Mr 2033 CL, morphine and pentazocine (ED_{50}) in different test models and species. Rb = rabbit.

According to Takemori (1976), the interactions of Mr 2033 CL, bremazocine, and morphine with the selective μ antagonist naloxone and the putative κ antagonist Mr 2266 CL were analyzed by means of the apparent pA_2-values in the Haffner test and the writhing assay in mice after subcutaneous administration (Tab. 1).

Agonist	Antagonist	Apparent pA_2		Potency ratio	
		Writhing	Haffner	Writhing	Haffner
Morphine	Naloxone Mr 2266 CL	7.76 7.15	7.52 6.45	4.1	11.7
Mr 2033 CL	Naloxone Mr 2266 CL	7.06 6.78	7.01 6.31	1.9	5.0
Bremazocine	Naloxone Mr 2266 CL	6.42 6.37	in- effective	1.1	-

Table 1. Apparent pA_2-values and potency ratios for the interactions of morphine, Mr 2033 CL and bremazocine with naloxone resp. Mr 2266 CL in two analgesic assays.

In the writhing test, naloxone is 4 times more potent than Mr 2266 CL as an antagonist of morphine and twice as potent in the case of Mr 2033 CL. Antagonizing bremazocine, both antagonists are equipotent. These data indicate that different receptor populations are involved in the analgesic effects of the three compounds in the writhing assay. The potency ratios characterize naloxone as the most potent antagonist in the Haffner test because Mr 2266 CL has a relatively low activity in this assay. The similarity of some of the apparent pA_2-values suggest that - in part - similar receptor populations may be responsible for the analgesic effects in both assays (Wüster et al. 1981).

2. Binding studies

Receptor binding studies with the two κ agonists Mr 2033 CL and bremazocine in membrane homogenates of rat brain resulted in similar binding properties of these two drugs, comparing their affinities to μ, κ and δ opioid receptor subtype (Tab. 2). In contrast to morphine and naloxone, which act predominantly via the μ receptor, Mr 2033 CL and bremazocine show high affinities to both, μ and κ receptors (Kosterlitz et al. 1981). According to the sodium shift, Mr 2033 CL should demonstrate some marked morphine antagonistic properties.

	μ receptor	κ receptor	δ receptor	Sodium Shift
morphine	1.4	9.0	37.0	12.5
Mr 2033 CL	0.7	1.3	2.6	3.6
bremazocine	1.0	1.8	1.4	1.1
naloxone	1.1	8.1	8.1	1.1
Mr 2266 CL	2.9	2.4	4.5	0.5

Table 2. Binding properties (k_i-values, [nM]) of morphine, Mr 2033 CL, bremazocine, Mr 2266 CL, and naloxone. Radioligand: μ receptor: ^{3}H-dihydromorphine, κ receptor: ^{3}H-ethylketazocine, and δ receptor: ^{3}H-D-Ala^2-D-Leu^5-enkephalin.

3. Morphine antagonistic effects

Morphine antagonistic effects of Mr 2033 CL have been found in different assays. Stereotypic circling movements and the Straub tail phenomenon induced by morphine were suppressed in mice. In morphine-treated rats, catalepsy was antagonized and in rabbits morphine-induced stupor was suppressed by Mr 2033 CL.

In morphine-dependent rats in the stage of withdrawal, exacerbation of abstinence was observed after administration of Mr 2033 CL. In non-withdrawn morphine-dependent dogs, Mr 2033 CL precipitated abstinence (Gilbert et al. 1977). The antagonistic potency of Mr 2033 CL ranged between that of nalorphine and that of naloxone in these experiments.

4. Side-effects

The strong analgesic effects of Mr 2033 CL were not accompanied by the Straub tail phenomenon or enhanced circling movements in mice. Mr 2033 CL did not induce catatonia in rats and stupor in rabbits in a morphine-like manner.

CNS-depressant effects of Mr 2033 CL were observed in different assays. In mice, the dose range of analgesia does not overlap with the dose range reducing aggression, exploration and locomotor activity.

In conscious rabbits, respiratory depression was weaker and of shorter duration than in animals treated with morphine. After stimulation of respiration in anaesthetized dogs by increasing arterial CO_2 tension, 1 mg/kg of Mr 2033 CL i.v. did not influence the respiratory minute volume, while 2 mg/kg of morphine i.v. provoked a pronounced depression.

The influence of Mr 2033 CL on the intestinal transit and the analgesic effects on the hot plate were tested in mice simultaneously. Mr 2033 CL reduced gut motility in a minor degree than morphine because it was 3 times more potent than morphine in reducing the intestinal transit, and 7 times more potent than morphine in the hot-plate test. Thus the analgesic ED_{50} of Mr 2033 CL did not inhibit gut motility completely, while the analgesic ED_{50} of morphine induced a complete inhibition.

In contrast to μ agonists, which cause urine retention, Mr 2033 CL and other κ agonists induce diuresis in unloaded rats (Fig. 2). In waterloaded animals Mr 2033 CL had an antidiuretic effect like morphine. The diuretic effect of Mr 2033 CL was not antagonized by naltrexone and might be explained by inhibition of ADH because the free water clearance increased significantly. The antidiuretic effect was antagonized by naltrexone in a morphine-like manner and might be a renal opioid effect. Concentration of plasma electrolytes and plasma osmolarity were not influenced with statistical significance.

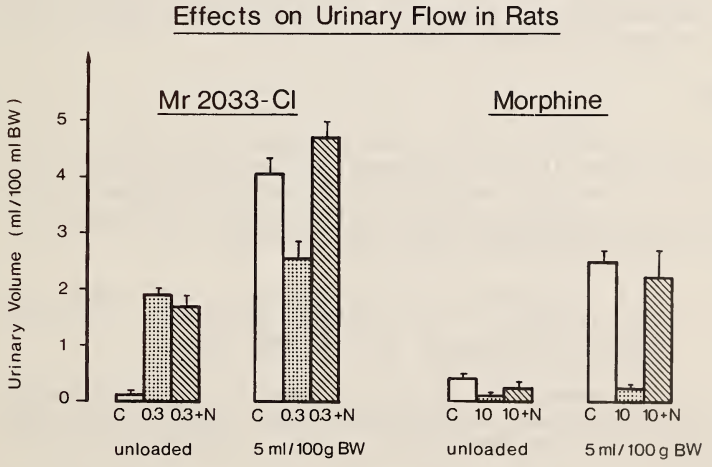

Figure 2. Effects of 0.3 mg/kg Mr 2033 CL and 10 mg/kg morphine on the urine excretion of rats, unloaded and water loaded with 5 ml/100 g body weight, and the antagonistic effects of naltrexone (= N). Mean values 2 hours after s.c. administration. C = saline control.

Dependence studies have been performed in rats, dogs and rhesus monkeys. Mr 2033 CL did not substitute for morphine in morphine-dependent animals of all three species. In the primary-dependence experiments in rats and rhesus monkeys, symptoms of withdrawal occurred, but these differed, both quantitatively and qualitatively, from those of morphine. Precipitation with nalorphine or naloxone provoked also a mild abstinence syndrome in both species. In self-administration studies in codeine-trained rhesus monkeys, Mr 2033 CL was not self-injected at rates above saline at any tested dose except one (Woods et al. 1979).

SUMMARY

Mr 2033 CL is a very potent non-morphine-like opioid analgesic as shown in different test models and animal species. On a weight for weight basis, it is about 20 times more potent than morphine. The analgesic effects of Mr 2033 CL are supposed to be different from those of morphine and bremazocine because of individual sensitivity against selective antagonists like naloxone and Mr 2266 CL. Mr 2033 CL does not induce the Straub tail phenomenon and increased circling movements in mice, catatonia in rats, and stupor in rabbits which are characteristic for μ agonists. Moreover, Mr 2033 CL does not have a morphine-like abuse potential in rats, dogs and rhesus monkeys. CNS-depressive effects were observed in different species. Respiratory depression and inhibition of intestinal transit seem to be of minor degree. In contrast to morphine, Mr 2033 CL provokes diuresis in rats. Binding studies in rats as well as dependence studies in rats and rhesus monkeys characterize Mr 2033 CL as a predominant κ agonist with morphine antagonistic properties.

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Preclinical Pharmacology of Metkephamid (LY127623), A Met-Enkephalin Analogue

Robert C. A. Frederickson, C. John Parli, Gary W. DeVane, and Martin D. Hynes

The structures of the two enkephalins, Met- and Leu-enkephalin, were reported in 1975 (9). There is convincing evidence that these peptides function in brain as neurotransmitters mediating or modulating various physiological functions including reaction to pain (5,8,14). These endogenous opioids could, therefore, provide the basis for development of specialized therapeutic entities but have no obvious clinical utility themselves. They are too rapidly degraded enzymatically to have any useful activity after systemic administration. Synthetic efforts, however, have produced analogues of the enkephalins which are more resistant to enzymatic degradation and which provide analgesic activity by the parenteral route. One such compound, which has been demonstrated to be an efficacious analgesic in the clinic is Metkephamid (LY127623). The preclinical pharmacology studies with this compound are reported in this paper. Preliminary accounts of some of this data have been reported previously (6,7).

METHODS

In Vitro Assays of Opioid Activity

IC_{50} values for inhibition of the electrically-induced (0.15hz, 1msec, 40v) twitch of the mouse vas deferens preparation by normorphine and metkephamid were determined as described previously (6). IC_{50} values were determined also for inhibition of the electrically-induced (0.8 hz, 0.7 msec, 40v) twitch of the guinea pig ileum preparation. The comparative affinities of metkephamid and morphine for μ and δ opioid receptors were determined by measuring the displacement of 0.25 nM [^{3}H]-naloxone and 0.75 μM ^{3}H-D-Ala-D-Leu-enkephalin, respectively, from freshly prepared homogenate of rat brain (10).

In Vivo Assays of Opioid Activity

The comparative ED_{50}'s of metkephamid, meperidine and morphine for producing analgesic activity in the mouse hot plate (6), mouse writhing (4,12) and rat tail jerk (12,13) tests were determined as

described previously (4,6,12,13). Mouse locomotor activity was measured in circular wire mesh cages. A light beam passed through the center of each cage and a count was registered each time a mouse interrupted one of these beams (11).

Assessment of Cross-Tolerance

Mice were made tolerant by treatment with 4 daily doses of morphine for 4 days as described previously (10). Control mice received saline on the same schedule. On day five, 16 to 20 hours after the last morphine injection, dose-response curves to morphine and metkephamid were generated in the mouse writhing assays.

Measurement of Placental Transport

Maternal femoral arteries in pregnant ewes were catheterized and fetal jugular veins and carotid arteries were also catheterized and externalized. When the animals had stabilized, metkephamid was given intramuscularly and maternal (10 ml) and fetal (7 ml) arterial blood samples were taken at 0, 10, 20, 30 and 45 minutes for later assay. Nineteen - twenty day pregnant female rats were decapitated and their blood collected in glass tubes. The fetuses were removed from the uterus and their blood was collected either after decapitation or via heart puncture using glass capillary tubes.

For the assay of metkephamid, one ml serum samples containing 6.72 mg NaF and 8.0 mg EDTA were precipitated with 2 ml of acetone. The supernatants were saturated with NaCl and extracted with ethyl acetate. The dried extracts were then derivatized with a Fluram solution and the resulting solution was subjected to reverse phase HPLC and fluorescence detection. For assay of meperidine, one ml serum samples containing 6.72 mg NaF and 8.0 mg EDTA were made basic with 0.1 ml of 1.0 M NaOH and extracted with diethyl ether. The dried extracts were dissolved in 0.3 ml of ethyl acetate and an aliquot was injected into a gas chromatograph containing a 5 ft. glass column packed with 3 percent OV-1 on 100/120 mesh Gas Chrom Q. The oven temperature was 165°C and the flame ionization detector's temperature was 250°C.

Drugs

Metkephamid was synthesized in the Lilly Research Labs as described previously (6).

RESULTS

Metkephamid produced potent naloxone-reversible depression of the electrically-induced twitch of both the mouse vas deferens and the guinea pig ileum. The IC_{50}'s for these effects are given in Table 1 together with the IC_{50} values for normorphine. pA_2 values for naloxone versus normorphine, Met-enkephalin and metkephamid on the mouse vas deferens preparation were determined to be 8.32 (9.06-8.69), 7.54 (7.38-7.74) and 7.60 (7.43-7.80), respectively. Also shown in Table 1 are the IC_{50} values for metkephamid and morphine for inhibition of the binding of ^{3}H-naloxone (^{3}H-Nx) and ^{3}H-D-Ala-D-Leu enkephalin (^{3}H-DADL) to rat brain homogenates.

TABLE 1

In Vitro IC_{50} Values (nM)

	Morphine (Normorphine*)	Meperidine	Metkephamid
A. Isolated tissues			
Mouse vas deferens (MVD)	390*	3900	5.4
Guinea pig ileum (GPI)	100*	1957	21.0
GPI/MVD	0.25	0.50	3.9
B. Inhibition of binding			
^{3}H-DADL	75	1814	4.4
^{3}H-Naloxone	6.5	460	2.5
^{3}H-Nx/3H-DADL	0.09	0.25	0.6

By the intraventricular route, the ED_{50} for metkephamid for analgesia in the mouse hot plate test was 1.5 pmoles/mouse. For comparison the ED_{50}'s for morphine and meperidine were 103 and 48000 pmoles, respectively. Metkephamid was also analgesic by systemic routes of administration. The ED_{50}'s after subcutaneous administration for metkephamid and several standards in the mouse hot plate and mouse writhing tests for analgesia are given in Table 2. By the intravenous route the ED_{50}'s for metkephamid and meperidine in the hot plate jump response were 0.21 (0.03-0.57) and 3.1 (1.4-5.7) μmole/kg, respectively, and on the hot plate hind paw lick response were 0.36 (0.08-0.05) and 1.7 (0.89-2.7) μmole/kg, respectively.

TABLE 2

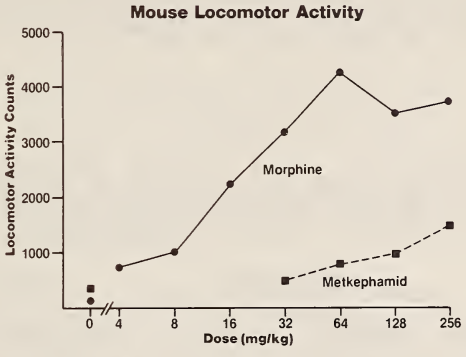
ED_{50}'s* (μmoles/kg, s.c.) in Analgesic Tests

	Mouse Hot Plate		Mouse Writhing
	Escape Jump	Hind Paw Lick	
Morphine	2.4	4.8	2.8
Meperidine	8.5	11.3	15.2
Metkephamid	0.2	1.5	5.5

*ED_{50}'s were determined at times of peak effect (30 minutes for morphine; 15 minutes for meperidine and metkephamid).

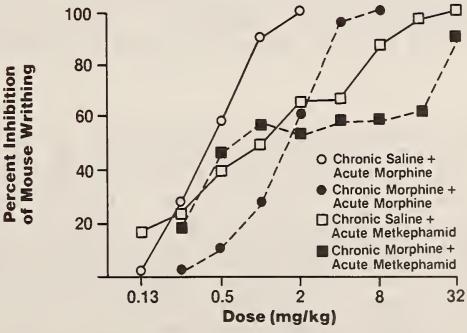
Comparison of the stimulation of mouse locomotor activity produced by metkephamid and morphine revealed marked differences. Morphine produced far greater locomotor activity in the 4 hour-test period than did metkephamid (Fig. 1).

FIGURE 1



The dose-response curve for morphine was shifted to the right after chronic administration of morphine, resulting in a 3.5-fold increase in the ED_{50} value for morphine (Fig. 2). A similar shift in the dose response curve was not observed for metkephamid in morphine-tolerant mice (Fig. 2).

FIGURE 2



The morphine dose-response curves were shifted to the right by 3 to 4-fold in the mouse hot plate hind paw lick and escape jump measures in mice treated 20 hours earlier with naloxazone (50 mg/kg, i.p.) compared to mice pretreated with saline. Such pretreatment with naloxazone produced no shift to the right of the dose-response curves to metkephamid.

The ability of metkephamid to cross the placental barrier was assessed by measuring maternal and fetal serum levels in sheep and

rats at various times after intramuscular injection of high doses of metkephamid. The data are summarized in Table 3. In the sheep, maternal serum levels of metkephamid after a dose of 5 mg/kg were 8-10 μg/ml at 10, 20 and 45 minutes after injection while fetal levels were undetectable at all times measured. The limit of sensitivity of the assay is 50 ng/ml so the ratio of fetal:maternal levels must be <1:200. In the rat the fetal:maternal ratio at 1 hr (time of peak blood levels) after metkephamid (50 mg/kg, s.c.) was about 1:60. The fetal:maternal ratio for meperidine, by contrast, was about 1:2.

TABLE 3

Maternal and fetal serum levels (μg/ml) of metkephamid and meperidine at various times after administration to sheep (intramuscular) and rats (subcutaneous).

		Metkephamid		Meperidine	
Species	Time (min)	Maternal	Fetal	Maternal	Fetal
1. Sheep	0	0.0	0.0		
	10	9.46±3.01	0.0		
	20	9.43±2.6	0.0		
	45	8.54±2.6	0.0		
2. Rat	60	7.17±0.28	0.12±0.04		
3. Rat	45			3.73±0.89	2.02±0.23

1. The dose of metkephamid was 5 mg/kg. 2. The dose of metkephamid was 50 mg/kg. 3. The dose of meperidine was 50 mg/kg.

DISCUSSION

Metkephamid (Tyr-D-Ala-Gly-Phe-N(Me)Met-NH_2) is an analogue of Met-enkephalin which has proved to be a very potent opioid ligand in various in vitro and in vivo assay systems. pA_2 analysis indicated that metkephamid utilized δ-receptors in the MVD and the ratio of IC_{50}'s on GPI versus MVD further supported a predominant, although not exclusive, action on δ-receptors. Surprisingly, however, this δ-selectivity was not seen in binding studies with brain homogenate. Metkephamid was much better (16X) than morphine at displacing the δ-ligand (^{3}H-DADL) in these studies but appeared roughly equieffective at displacing a μ-ligand (^{3}H-Nx). One explanation for these apparently disparate findings might be that metkephamid has much greater efficacy at the δ-receptor than at the μ-receptor.

Analgesic data supports the concept that Metkephamid acts on a different receptor (presumably the δ-receptor) than does morphine. On a molar basis metkephamid was at least 100X more potent than morphine at producing analgesia after administration into the lateral ventricles and was about 10X more potent than meperidine after intravenous administration. After subcutaneous administration

metkephamid was more potent than morphine and meperidine in the mouse hot plate test for analgesia and was intermediate in potency between morphine and meperidine in the mouse writhing test for analgesia. Both metkephamid and meperidine were considerably less potent than morphine, however, on the rat tail jerk test. ED_{50}'s for metkephamid and meperidine in this test were not calculated because of the very shallow dose-response curves. Analgesic testing in morphine-tolerant mice revealed a relative lack of cross-tolerance to metkephamid. Similar findings have been reported for morphine-tolerant rats and monkeys (15). These findings indicate a different mechanism of action for Metkephamid which most likely involves production of analgesia by an action on δ-receptors, as well as on the μ-receptors utilized by morphine. The latter mechanism appears to become more prominent at higher doses. This concept is supported also by the selective antagonism of morphine analgesia without effect on metkephamid analgesia by pretreatment with the appropriate dose (50 mg/kg, i.p.) of naloxazone.

It was reported previously that metkephamid produces much less physical dependence relative to its analgesic activity than do standard analgesics such as morphine, meperidine or pentazocine (6,7). This is confirmed here by the relative inactivity of metkephamid compared to morphine on locomotor activity in mice. This measure is a reflection of physical dependence potential.

Studies on placental transport in sheep and rats have revealed a dramatic advantage for metkephamid for potential use in obstetric analgesia. Very little, if any, metkephamid appears to cross the placental barrier compared to an almost 1:1 transport for meperidine.

Metkephamid has been tested in man also (6,7) and clinical studies have demonstrated analgesic efficacy for this unique new compound (see eg. 1,2,3,).

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Development of Orally Active Cannabinoids for the Treatment of Glaucoma

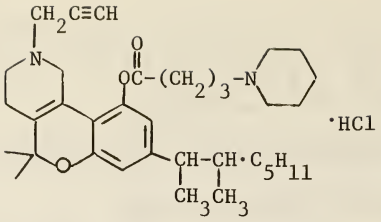
Raj K. Razdan, John F. Howes, and Harry G. Pars

Glaucoma is one of the major causes of blindness in the world. It is a condition of the eye where higher than normal intraocular pressure (IOP) progressively affects the field of vision resulting in irreversible blindness. Early observations by Hepler and Frank (1971) demonstrated that smoking marijuana resulted in a decrease of IOP in normal subjects. Several reports have since appeared confirming the IOP-lowering effects of marijuana or Δ^9-THC in both normal subjects (Hepler et al. 1972; Shapiro 1974; Perez-Reyes et al. 1976; Cooler and Gregg 1977) and glaucoma patients (Hepler et al. 1976; Lockhart et al. 1977) and are reviewed elsewhere (Razdan and Howes 1980). Although Δ^9-THC has been reported to lower IOP in animals when administered topically, these results have not been confirmed in glaucoma patients (Merritt et al. 1981; Green and Roth 1982).

As part of an ongoing program in our laboratories to develop new chemical entities derived from the cannabinoid nucleus as potential drugs (Meltzer et al., 1981; Pars et al. 1977), we describe in this paper two compounds, Nabitan (SP-106) and Naboctate (SP-325), which reduce IOP in animals and in man and are potential antiglaucoma drugs.

Drugs from the cannabinoid class produce a number of side effects such as tachycardia, orthostasis and subjective CNS effects which could limit their therapeutic use. The objective of our development program has been to prepare a compound in which a good separation of therapeutic and side effects exists. To achieve these goals, we have looked for lowering of intra-ocular pressure in animals, combined with a low incidence of tachycardia. Identified candidates were then evaluated clinically.

Our earliest evaluations were with Nabitan (Razdan et al. 1976). This has been studied by Weber et al. (1981) and Tiedeman et al. (1981).



Nabitan (SP-106; BW1464)

Table 1 shows the decrease in intra-ocular pressure observed in normotensive human volunteers (Weber et al. 1981). The falls in IOP are small but none of the subjects in this study had a starting IOP of greater than 18.0mmHg.

Table 1. Changes in Intra-ocular Pressure Due to Nabitan*

Treatment	No. of Eyes	Change in IOP 1hr	2hr	4hr	6hr	8hr	24hr
Placebo	20	-0.80 ±0.40	-1.45 ±0.28	-1.40 ±0.28	-1.90 ±0.37	-1.25 ±0.36	-0.35 ±0.33
5 mg	6	-1.00 ±1.32	-2.83 ±1.01	-3.17[a] ±0.31	-3.50 ±1.18	-2.83 ±0.87	-0.50 ±0.34
10 mg	6	-0.83 ±0.75	-1.83 ±1.19	-2.83 ±1.65	-3.17[c] ±0.91	-1.67 ±0.76	+1.33 ±0.71
15 mg	12	-0.58 ±0.40	-2.58 ±0.53	-3.42[a] ±0.45	-2.25 ±0.79	-2.00 ±0.63	+0.25 ±0.07
20 mg	6	-1.67 ±0.88	-3.33 ±1.56	-2.83[b] ±1.30	-2.50 ±1.59	-2.50 ±1.98	+0.33 ±0.56

*By the Mann-Whitney two-sample rank test, from Goldstein, A.: Biostatistics, An Introductory Text. New York, Macmillan, 1964, pp. 55-59.

[a] $p \leqslant 0.005$ when compared to placebo controls

[b] $p \leqslant 0.01$

[c] $p \leqslant 0.05$

At high doses, Nabitan caused a mild tachycardia (Weber et al. 1981). Subjects receiving 10mg or more reported marijuana-like side effects.

In a further clinical study on ocular hypertensives, Nabitan showed a lowering of IOP (Figures 1, 2 and 3). This was a double masked study carried out over a period

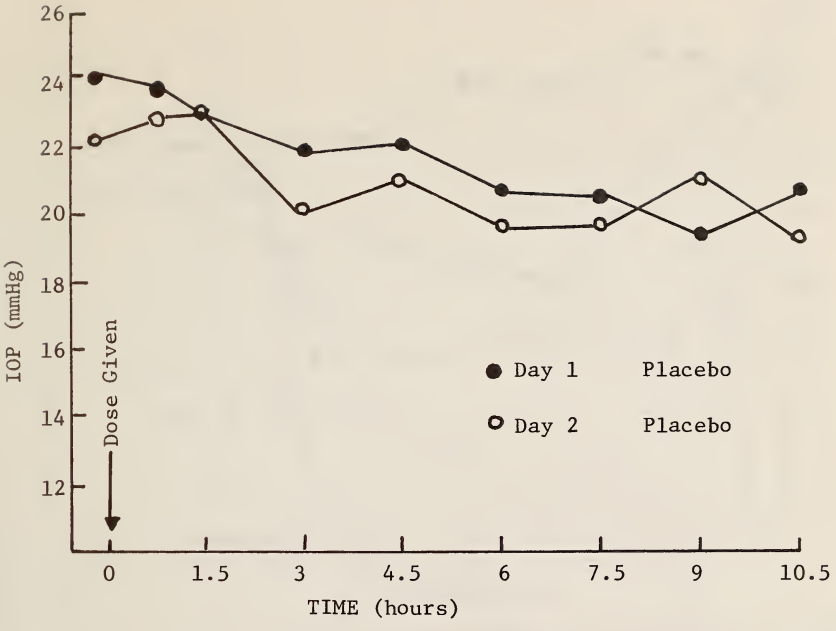
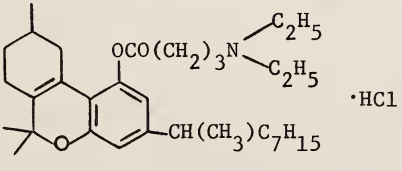


Fig. 1. Mean IOP Placebo Subgroup Nabitan (12 eyes)

of two days. On the first day, the subject received only placebo; on the second day either a placebo or the test drug. The results show that Nabitan caused a dose-related fall of IOP. Mild tachycardia was observed and some incidents of orthostasis occurred.

In an effort to reduce the cardiovascular side effects a different compound, Naboctate (SP-325) was developed (Razdan and Howes 1981).



Naboctate (SP-325)

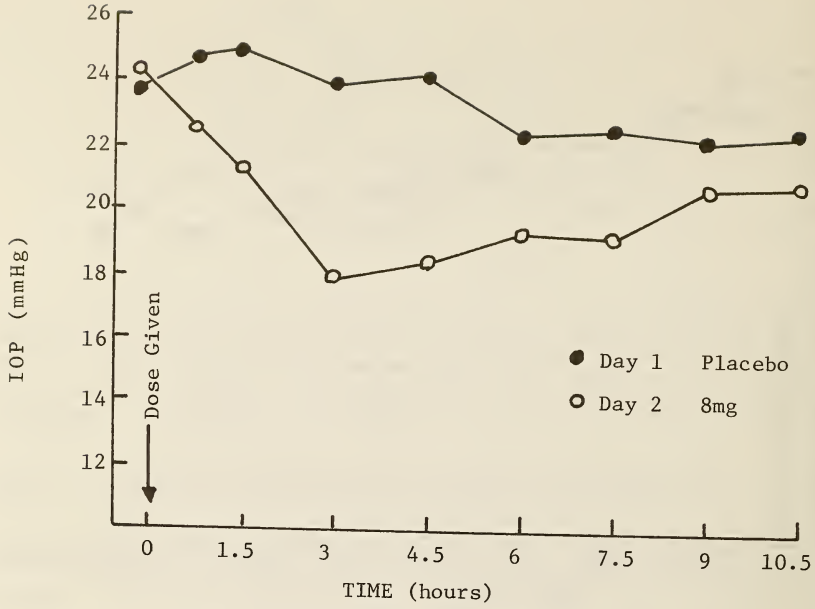


Fig. 2 MEAN IOP 8mg NABITAN (20 eyes)

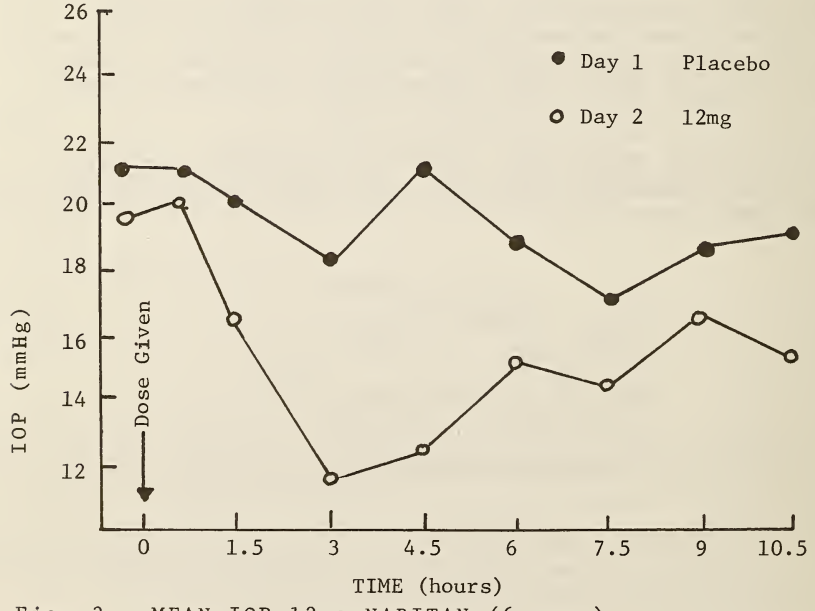


Fig. 3 MEAN IOP 12mg NABITAN (6 eyes)

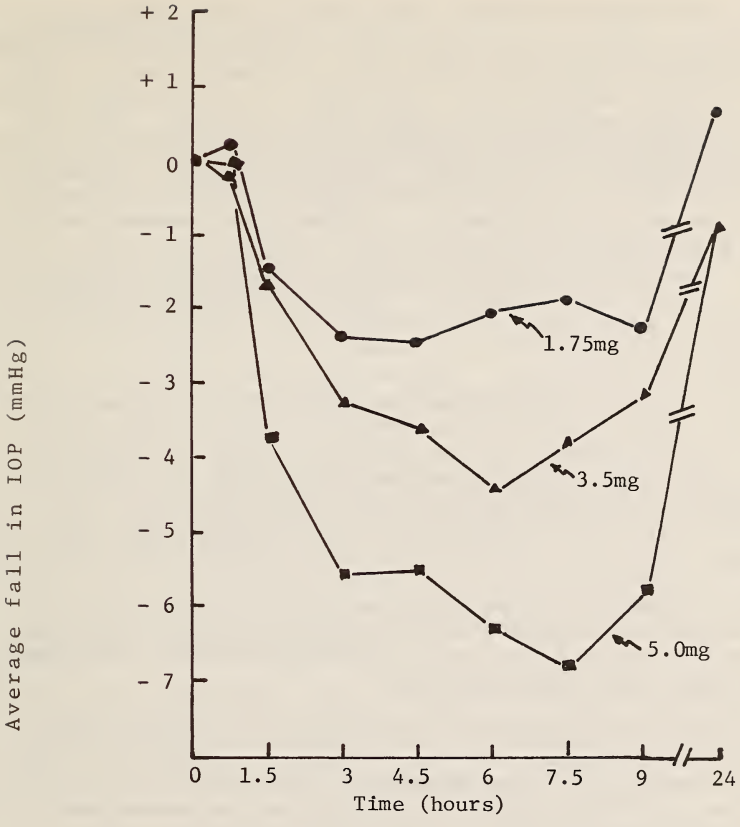


Fig. 4 Mean fall in IOP vs time for normal subjects.

Naboctate (SP-325) lowered the intra-ocular pressure of normotensive rabbits at doses of 5, 10 and 20mg/kg orally. The peak effect was observed after 3 hours at which time a dose-related response was observed. The duration of action in these experiments was about 6 hours. SP-325 caused a slight increase in heart rate in conscious rats given doses of 5, 10 and 20mg/kg orally. A small non-dose-related hypotension was observed at 3 1/2 to 5 1/2 hours in these animals. In the anesthetized animal, no significant cardiovascular effects were observed. SP-325 did not affect respiratory parameters in any of these experiments. When challenges of neurotransmitters were used, SP-325 exerted a weak anticholinergic effect.

The acute LD_{50} (p.o.) in the rat and the rabbit was >1500 and >1000 mg/kg respectively. In a 30-day subchronic study using rats and rabbits, SP-325 caused behavioral effects, which disappeared by the end of the first week. These included ataxia and sedation. No gross pathology was observed and microscopic analysis of tissues revealed no drug-related pathological changes.

In normal volunteers Naboctate was well tolerated and caused a dose-dependent decrease in IOP (Figure 4). In this limited study there was a notable absence of cardiovascular and CNS side effects.

We conclude that marijuana and synthetic cannabinoids appear to have a place in the therapy of glaucoma. The two cannabinoids we have examined lower IOP when administered orally. Naboctate is potent in normotensive subjects and appears to be free of major side effects. This drug is currently under development for the treatment of glaucoma.

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Dependence Studies on Zopiclone

Tomoji Yanagita and Shin Kato

INTRODUCTION

Zopiclone is a nonbenzodiazepine hypnotic developed by Rhone-Poulenc France, which is known to act through the benzodiazepine receptors and shows a benzodiazepine-like pharmacodynamic profile. Its chemical name is 6-(5-chloro- 2-pyridyl)-7-((4-methyl-1-piperazinyl) carbonyloxy)-6,7-dihydro-(5H)-pyrrolo(3,4-b)pyrazine-5-one.

METHOD

Experiment 1. GROSS BEHAVIORAL OBSERVATION OF THE ACUTE CNS EFFECTS OF ZOPICLONE AND DIAZEPAM IN NORMAL MONKEYS. Single doses of intravenous and intragastric zopiclone and intragastric diazepam were administered to normal rhesus and crab-eating monkeys, and gross behavior was observed until the drug effects disappeared.

Experiment 2. CROSS PHYSICAL DEPENDENCE TEST ON ZOPICLONE IN BARBITAL-DEPENDENT AND WITHDRAWN MONKEYS. The suppressive effects of zopiclone and diazepam on the barbital withdrawal signs were observed in rhesus monkeys that had been made physically dependent on barbital by twice daily intragastric doses of barbital 75 mg/kg for 3 months or longer and withdrawn for 28-30 hrs. The severity of the withdrawal signs was graded by our criteria (Yanagita & Takahashi 1970).

Experiment 3. PHYSICAL DEPENDENCE-PRODUCING TEST IN NORMAL MONKEYS. Zopiclone 16 mg/kg was intragastically administered twice daily for 4 weeks to 4 normal crab-eating monkeys, followed by a withdrawal test on week 5. Administration was thereafter immediately reinitiated at the same dose as before for 2 weeks, and at 32 mg/kg twice daily for 2 more weeks, with a second withdrawal test during the next week. Gross behavior, body temperature, and weight were observed regularly during administration periods, and withdrawal signs were observed several times daily during the withdrawal periods. Similar experiments were conducted with diazepam in crab-eating monkeys and with nitrazepam in rhesus monkeys, the doses being shown in table 1.

Experiment 4. CONTINUOUS INTRAVENOUS SELF-ADMINISTRATION OF ZOPICLONE. This experiment was conducted in 4 rhesus monkeys. An intravenous catheter was connected through the restraint arm to an auto-

matic injector, each lever-press activating the injector to deliver a predetermined unit dose of zopiclone at infusion volume 0.25 ml/kg and speed 24-26 sec/ml. Two monkeys had had previous experience with self-administration of the reinforcing stimulant lefetamine and/or other drugs and had been rested from any experiment for 1 month or longer. The other 2 naive monkeys were first tested with saline until the daily intake rate became low and stable, then with zopiclone. The unit doses and period observed are shown in table 2.

Experiment 5. CONTINUOUS INTRAGASTRIC SELF-ADMINISTRATION OF ZOPICLONE AND DIAZEPAM. Intragastric self-administration of zopiclone and diazepam was tested in 4 rhesus monkeys each as in Experiment 4 . Here the unit volume was 1 ml/kg and infusion speed was 13-18 sec/ml. The unit doses and period observed are shown in tables 3 and 4.

RESULTS

Experiment 1. By intravenous administration of zopiclone 0.25 mg/kg 1 out of 2 monkeys exhibited slow movements and diminished spontaneous motor activity. These signs disappeared in about 1 hr. At 1 mg/kg, marked motor impairment and hyporeactivity were noted. At 4 mg/kg the intensity of the above signs remained the same although the duration of the effect was extended. With the crab-eating monkeys, zopiclone 1 and 4 mg/kg produced practically the same results as with the rhesus monkeys. With single intragastric administrations of zopiclone to rhesus monkeys, slowed movement was seen at 4 mg/kg from 30 min after administration, followed by motor impairment, diminished spontaneous motor activity, and hyporeactivity. The intensity and duration of the drug effects reached a plateau at 16 mg/kg. In crab-eating monkeys single doses of 4 and 16 mg/kg produced slightly less intense and shorter lasting signs than with rhesus monkeys. Single intragastric doses of diazepam 1 mg/kg in crab-eating monkeys produced hyporeactivity and slight slowing of movement. At 4 mg/kg, hyporeactivity and motor impairment were seen.

Experiment 2. At 28.5 hr after the final administration of barbital all monkeys showed such signs as apprehension, hyperirritability, piloerection, tremor, abdominal muscular rigidity, and motor impairment. Some monkeys additionally showed clonic convulsions. Single doses of intragastric administration of zopiclone 4 mg/kg lessened most of the withdrawal signs, and 8 mg/kg suppressed the signs nearly completely. At 16 mg/kg the signs were completely suppressed at 0.5 hr after administration. With diazepam the suppression was incomplete at 4 mg/kg but complete at 8 mg/kg. The complete suppression continued for 1 hr with zopiclone and for 3 hrs with diazepam.

Experiment 3. In repeated administration of zopiclone the monkeys showed depressed signs as described in Experiment 1. On day 7, all monkeys showed less pronounced signs than on the first day, but from day 14 on there was no noteworthy change in severity. In the 1-week withdrawal test, monkeys showed apprehension, hyperirritability, tremor, piloerection, and increased muscular rigidity of the limbs from

the 2nd day, with the peak signs on day 3 or 4 and gradual lessening thereafter. Extremely moderate body weight loss was noted in 3 out of 4 monkeys during this period, and rise in body temperature was confined to 1 C or less, so that the withdrawal signs were graded as intermediate in all monkeys (table 1). The administration was resumed thereafter for the 2nd test. On day 7, the severity was the same as or less than that on the last day of the 1st administration period. Due to further lessening on day 14, the doses were increased to 32 mg/kg twice daily from day 15. On day 15 the severity increased in all monkeys, lessening again in a week to near that on day 14 and continuing at this level to the end of the second administration period. The following 1 week of withdrawal observation showed signs in all 4 monkeys to be nearly the same as before.

Table 1 Development of Physical Dependence in Monkeys

Drug	Monkeys	Dose (mg/kg i.g. x 2/day)		Withdrawal signs* ( ) : No. of monkeys	
		1 st 4 wks	2 nd 4 wks	1 st (5 th wk)	2 nd (10 th wk)
Zopiclone	4 Crab-eating	16	16-32	Intermediate (4)	Intermediate (4)
Diazepam	4 Crab-eating	4-8	8	Intermediate (2) Severe (2)	Intermediate (1) Severe (3)
Nitrazepam	4 Rhesus	4	4-8	Intermediate (4)	Intermediate (4)

* : Severest grade during 7-day withdrawal period.
"Intermediate" includes hyperirritability, restlessness, tremor, and impaired motor activity, and "severe" includes convulsions.

With diazepam, depression less severe than on the 1st day was observed on day 14 with shortened duration of effect in all monkeys. Doubling the doses from day 15 produced somewhat severer depressive signs and longer duration of effect, but the severity decreased again on day 21 or 28. In the 1st withdrawal test, apprehension, hyperirritability, tremor, and piloerection were observed in all monkeys, with convulsions in 2 out of 4 monkeys on day 6. No body weight decrease exceeded 10 percent, and no body temperature increase exceeded 1 C. The withdrawal signs were thus graded as severe and intermediate in 2 monkeys each. In the 2nd administration period the effects of the drug gradually weakened as observed on days 7, 14, 21, and 28. During the 2nd withdrawal test convulsions occurred in 3 out of 4 monkeys on days 3, 6, and 7. The body weight of 1 monkey decreased 12 percent, but changes in the other 3 remained within 10 percent. This time the grade was severe in 3 monkeys and intermediate in 1.

In the case of nitrazepam all monkeys showed gradual decrease in severity of the depressive signs throughout the 4-week administration period, with a major decrease in the 1st week. In the withdrawal test, all monkeys showed apprehension, muscular rigidity of the limbs, hyperirritability, and/or tremor from the 2nd day, peaking on day 4 in all monkeys, gradually lessening thereafter. Loss of body weight did not exceed 10 percent and no body temperature rise was ob-

served; thus the withdrawal signs were graded as intermediate in all monkeys. On day 14 of the 2nd administration period the depressant effects weakened beyond the level on the last day of the 1st period. When doses were increased to 8 mg/kg from day 15, the intensity increased in all monkeys, but it was still weaker on day 21 than on day 21 of the 1st period, and the intensity stayed at this level until the end of the administration period. The 2nd withdrawal test showed results in all 4 monkeys similar to those observed in the 1st test.

Experiment 4. The 2 experienced monkeys (Nos. 742, 1026) self-administered saline at low rates (table 2). In self-administration of zopiclone 0.25 mg/kg/inj, the animals took respective daily averages of 75.3 and 34.1 injections in the 1st 2 weeks, increasing in the next 2 weeks. Replacing with saline for 2 days, No. 742 intook 36 and 18 times on days 1 and 2. No. 1026 intook 154 times on day 1. Returning to zopiclone produced further increase of daily intake rates in them. These monkeys initially exhibited reduced responsiveness to the observers, decreased spontaneous motor activity, and motor impairment, but the signs gradually weakened from week 2. In the final 1-week saline test intake reduced markedly from day 2 and such mild withdrawal signs as hyperirritability and tremor were observed. One of the naive monkeys (No. 1062) maintained daily average intake at 32.0 with the unit dose of 0.25 mg/kg for the 2 weeks, while the other (No. 1063) did not. The unit dose for No. 1063 was thus raised to 1.0 mg/kg, with a resulting increase in the daily average over 2 weeks to 24.0, then to 34.8 in the next 2 weeks. In 2 days of withdrawal with saline, both monkeys exhibited a rapid decrease in intake on day 2. When zopiclone was resumed at 0.25 mg/kg in both monkeys fairly stable intakes were observed. During the final 1 week with saline, rapid decrease in intake was noted and the mild withdrawal signs were observed.

Table 2

Continuous Intravenous Self-administration of Zopiclone in Rhesus Monkeys

Monkey	Average daily number of self-administrations (per 1 or 2 wks)						
	Saline	Zopiclone (mg/kg/inj)		Saline	Zopiclone (mg/kg/inj)		Saline
		0.25	1.0		0.25	1.0	
	1 wk	4 wk	4 wk	2 days	4 wk	4 wk	1 wk
No. 742 Experienced	2.0	75.3-73.9	— —	36, 18	93.1-96.9	— —	68, 14
No. 1026 Experienced	5.4	34.1-52.0	— —	154, 26	54.2-65.2	— —	63, 9
No. 1062 Naive	7.3	32.0-63.4	— —	76, 11	69.8-83.9	— —	42, 23
No. 1063 Naive	3.7	2.8 —	24.0-34.8	80, 12	— —	34.9-37.2	46, 22

Experiment 5. In intragastric self-administration of zopiclone at 1 mg/kg, 3 out of 4 monkeys self-administered the drug at higher daily rates than for CMC; however, these rates were less than 10, although different unit doses were tested (0.25, 0.5 and 2.0 mg/kg; table 3).

No. 256 did not show any intake during the 12-week test period in spite of programmed forced administration of the drug for 2 weeks. In 3 days of withdrawal with CMC, No. 595 extinguished the drug-taking behavior without any increase of intake, but Nos. 755 and 1000 showed obvious rate increase and mild withdrawal signs. During active self-administration periods in the 3 monkeys, only moderate depressive signs were observable. In a final 1 week of withdrawal, a slight increase of CMC intake was observed in Nos. 595 and 1000, and some increase similar to the previous withdrawal was observed in No. 755. Again only mild withdrawal signs were observed.

Table 3

Continuous Intragastric Self-administration of Zopiclone in Rhesus Monkeys

Monkey	Average daily number of self-administrations (per 1 or 2 wks)								
	0.5% CMC	Zopiclone (mg/kg/inj)				CMC	Zopiclone		CMC
	1 wk	1.0 4 wk	0.25 2 wk	1.0 2 wk	2.0 4 wk	3 days	2.0 6 wk	0.5 4 wk	1 wk
No. 256	0	0	–	–	0	–	0	–	0
Experienced		–			0*		0.7		
							0.1		
No. 595	3.1	8.9	6.0	2.4	5.9	1.0	3.5	8.6	8.7
Experienced		–			4.2		–	6.9	
							–		
No. 755	0	4.1	–	–	6.4	16.3	7.8	8.7	11.9
Experienced		6.3			9.4		7.7	2.9	
							–		
No. 1000	1.3	4.6	5.1	–	6.6	13.3	5.0	1.7	4.3
Experienced		6.1			4.1		2.9	3.6	
							–		

* : Programmed administration added (2 mg/kg every 3 hrs)

Table 4

Continuous Intragastric Self-administration of Diazepam in Rhesus Monkeys

Monkey	Average daily number of self-administrations (per 1 or 2 wks)								
	0.5% CMC	Diazepam (mg/kg/inj)				CMC	Diazepam		CMC
	1 wk	0.25 4 wk	1.0 2 wk	0.25 2 wk	1.0 4 wk	3 days	1.0 4 wk	2.0 2 wk	1 wk
No. 433	0.1	4.5	4.9	5.1	8.7	3.3	2.3	–	3.1
Experienced		2.1			3.6		2.1		
No. 828	4.7	4.9	3.4	2.1	10.1	14.3	9.9	–	12.7
Experienced		–			6.4		5.9		
No. 993	4.3	1.4	1.2	–	1.8	1.7	1.0	0.1	0.4
Experienced		–			0.6		–		
No. 1062	3.3	5.9	3.1	–	2.1	1.7	5.4	2.5	2.1
Experienced		–			3.2		2.3		

In the experiment on diazepam also, 3 out of 4 self-administered the drug at relatively low rates at unit doses of 0.25 and 1.0 mg/kg (table 4). The daily rates increased in Nos. 433 and 828 when the unit dose was again increased to 1 mg/kg, but the rates gradually decreased thereafter. In 3 days of withdrawal, the daily rate of No. 828 increased but the rates of the other monkeys were low. During the active self-administration periods the monkeys showed CNS depressive signs that were not so prominent. In the final 1 week with CMC, only No. 828 showed meaningful increase of intake rate and manifested mild withdrawal signs.

DISCUSSION

In the present study, crab-eating monkeys were used in some, and rhesus monkeys in most of the studies. The reason for this was the short supply of rhesus monkeys; however, in Exp. 1 not much species difference was found between them regarding susceptibility to the CNS effects of zopiclone. The acute CNS effects of zopiclone quite resemble those of diazepam in both rhesus and crab-eating monkeys. The minimum effective doses from gross behavioral observation were less than or roughly equal to 0.25 mg/kg i.v. and 4 mg/kg i.g. The i.g. effect reached a plateau at 16 mg/kg, reflecting a characteristic dose-response relationship of many benzodiazepines (Yanagita 1981). Duration of effect was generally short in comparison to diazepam, particularly at large doses. For reference, the respective minimum effective doses of diazepam and nitrazepam in rhesus monkeys have been reported as 1.0 and 0.2 mg/kg i.g. (Yanagita et al. 1975, Kato & Yanagita 1981).

Zopiclone suppressed barbital withdrawal signs incompletely at 8 mg/kg and completely at 16 mg/kg. Diazepam 4 and 8 mg/kg were equipotent to zopiclone 8 and 16 mg/kg in this respect. The duration of complete suppression by zopiclone was considerably shorter than with diazepam. The cross physical dependence potentials of both drugs to barbital appear to be nearly parallel to the potencies of the CNS depressant effects. In physical dependence-producing tests, however, diazepam showed higher potential to produce physical dependence than zopiclone in crab-eating monkeys, since severer withdrawal signs were found with diazepam in both withdrawal tests. With zopiclone, the development of physical dependence appeared to have reached to a maximum level in the 1st 4-week period, since no increase of withdrawal severity was observed in the 2nd test. The potential of zopiclone appeared to be similar to nitrazepam. During repeated administration of zopiclone, diazepam, and nitrazepam, obvious development of tolerance to the CNS depressant effects was observed in the monkeys' gross behavior. With zopiclone, however, the tolerance development tended to reach a maximal level relatively early.

It was quite evident that zopiclone possesses reinforcing effect, especially when self-administered intravenously. The higher daily response rate than for diazepam by this administration route may be attributable to the shorter duration of effect. In contrast, with

pentobarbital (Yanagita & Takahashi 1973), no marked depressive signs such as severe motor impairment or light anesthesia were observed during the active intravenous self-administration period with zopiclone, nor were severe withdrawal signs observed when the drug was replaced with saline. In intragastric self-administration, however, the daily rates were generally low regardless of unit dose, although weak reinforcing effect has been demonstrated with the drug. These results were very similar to the results with diazepam.

Thus the dependence potential of zopiclone was regarded to be weaker than that of diazepam and nearly equal to that of nitrazepam physically, and comparable to that of diazepam psychologically.

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Dissociation of the Rewarding and Physical Dependence-Producing Properties of Morphine

Michael A. Bozarth and Roy A. Wise

Addiction to opiates is usually characterized by the repetitive intake of large quantities of drug and the development of marked physical dependence. Although recent definitions of drug addiction emphasize the behavioral aspects of compulsive drug intake (e.g., Eddy, 1973; Jaffe, 1975), several theories of opiate addiction have postulated that the development of physical dependence is essential for establishing compulsive drug use (e.g., Dole, 1980; Lindesmith, 1980; Spragg, 1940; Wickler & Pescor, 1967). Specifically, the withdrawal discomfort produced by the discontinuance of opiate intake in physically dependent persons has been postulated to provide the motivation to ingest opiates by relieving the distress produced by abstinence. This negative reinforcement model of addiction seems to fit with many of the patterns of opiate intake, but it fails to account for the initial acquisition of drug-taking habits. Nonetheless, the notion that opiate addicts self-administer drugs to alleviate withdrawal distress remains a very popular view.

The self-administration of drugs by laboratory animals has suggested that many of the substances abused by humans can serve as positive reinforcers (Seiden & Dykstra, 1977; Woods & Schuster, 1968). Although some early studies of animal self-administration used subjects that were made physically dependent on an opiate prior to testing for self-administration (e.g., Weeks, 1962), later studies have shown that naive subjects will also learn and sustain self-administration of opiates at dose levels that do not produce obvious physical dependence. On the other hand, it has been shown that physically dependent animals will work to avoid injections of narcotic antagonists that precipitate withdrawal (Goldberg et al., 1972). Thus it seems that negative reinforcement (i.e., the avoidance of withdrawal distress) is also capable of maintaining behavior. This has led to controversy regarding the relative importance of positive and negative reinforcement mechanisms in maintaining opiate intake in human addicts. Even studies reporting the absence of clear signs of physical dependence in animals self-administering opiates cannot rule out the possibility that the animals are experiencing some withdrawal discomfort during periods of abstinence.

One approach to studying the relative contribution of the positive and negative reinforcing properties of opiates to the maintenance of drug intake is to identify the underlying neural substrate of

each component and differentially manipulate them to assess their impact on behavior. Usually, however, it is not possible to produce physical dependence without the concomitant positive reinforcing properties of opiate or to test for positive reinforcement without the possibility that some degree of physical dependence has developed as a consequence of drug intake. We report here the results of two lines of investigation designed to determine the relationship between opiate reward and the development of physical dependence. The first experiment was designed to determine if the opiate receptor field responsible for positive reinforcement is also involved in physical dependence and a second experiment was designed to assess the rewarding properties of a single injection of heroin. These studies should help to clarify the importance of physical dependence in drug-taking behavior by examining the degree to which positive reinforcement and physical dependence mechanisms can be dissociated.

EXPERIMENT I: Physical Dependence From Central Morphine Injections

Wei (1981) and Wei and Loh (1976) have reported that rats chronically infused with morphine into the periaqueductal gray-fourth ventricle region show pronounced withdrawal signs when challenged with the narcotic antagonist naloxone. In these studies, morphine was infused chronically using an osmotic minipump (Alzet Corp.) and various withdrawal signs were measured following a challenge dose of naloxone. Although a variety of withdrawal signs are demonstrable after central morphine injections, the most clear appear to be escape attempts from a cylindrical enclosure, teeth chattering, and wet-dog shakes. We have used the procedure described in Wei (1981) to study the ability of morphine injected into the ventral tegmental area to produce physical dependence in rats. This brain region has previously been shown to contain the opiate receptor population that is critical for the rewarding properties of morphine (Bozarth & Wise, 1980, 1981a, 1982; Britt & Wise, 1981; Phillips & LePiane, 1980). The effects of chronic morphine injections into other brain regions were also assessed to determine the locus of the opiate receptor field mediating the development of physical dependence.

Method

Male Long-Evans rats (weighing 300-375 g) were stereotaxically implanted with 21 gauge cannulae aimed at the various brain regions listed in Table 1. While the rats were anesthetized with sodium pentobarbital (60 mg/kg), cannulae filled with morphine were connected to osmotic minipumps and the cannula tips lowered to the brain region under study. The minipumps delivered 1.0 ul/hr of 1.5 nmole/ul morphine sulfate dissolved in Ringer's solution. The minipumps were implanted subcutaneously between the scapulae of the animals and polyethylene tubing was used to connect the minipumps to the implanted cannulae (see Wei, 1981, for details).

After 72 hours of continuous drug infusions, the rats were chal-

lenged with an intraperitoneal injection of naloxone hydrochloride (5.0 mg/kg) and placed in a Plexiglas cylinder (23 x 25 cm). The presence of teeth chattering, wet-dog shakes, and the number of escapes from the cylinder were scored in five minute segments for the next 20 minutes. Other withdrawal signs were also observed but no attempt was made to quantify them since they have been shown to be more variable than the measures assessed in this study (see Wei et al., 1973).

	anterior-posterior[1]	lateral[2]	ventral[3]	animals tested
VTA	-3.8	±0.6	7.8	12
VTA$^{30^0}$	-3.8	±0.6	8.8	19
PVG-R	-3.8	±0.6	5.8	14
D3V	-3.8	±0.0	4.9	13
PVG-C	-6.8	±0.0	4.5	20

Table 1: Stereotaxic coordinates used for central morphine infusions (adapted from Pellegrino et al., 1979). VTA: ventral tegmental area; VTA$^{30^0}$: ventral tegmental area with cannulae angled 20 to 30^0 from the midline to avoid the PVG; PVG-R: rostral periventricular gray substance; D3V: central aspect of the dorsal third-ventricle; PVG-C: caudal periventricular gray-Aqueduct of Sylvius. [1]mm from bregma; [2]mm from the midline; [3]mm from dura.
(Pellegrino, L.J.; Pellegrino, A.S.; and Cushman, A.J. A Stereotaxic Atlas of the Rat Brain, 2nd edition, 1979. New York, Plenum Press.)

Results and Discussion

Injections into either the rostral or caudal regions of the periventricular gray substance produced marked physical dependence as reflected in escape behavior (see Figure 1). The animals with cannulae in the ventral tegmental area also demonstrated significant escape behavior, although at about one third the frequency of subjects injected with morphine into the rostral periventricular gray region. When morphine was injected into the dorsal aspect of the third ventricle, few escapes were seen after the naloxone challenge. Other signs of physical dependence were also observed in the rats injected with morphine in the periventricular gray regions: teeth chattering was seen with equal frequency in these two sites (26.2% vs. 26.7%), but wet-dog shakes were primarily observed following infusions into the caudal periventricular gray region (36.2% vs. 12.5%). This supports the notion that different brain regions may be involved in the production of different signs of physical dependence (e.g., Wei et al., 1973) and cautions against consideration of the withdrawal syndrome as a unitary phenomenon generated by a single brain mechanism. The fact that morphine infusions into the central aspect of the dorsal third-ventricle did not produce physical dependence suggests that the dependence resulting from rostral periventricular gray infu-

sions was due to a local drug action and independent of ventricular diffusion.

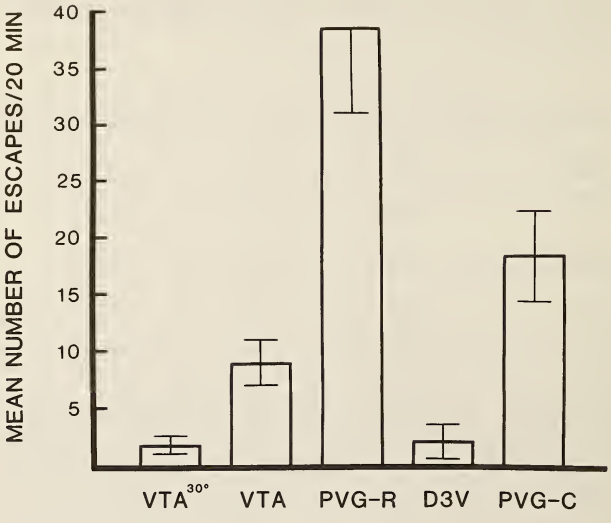

Figure 1: Mean (±SEM) number of escapes in 20 minutes following naloxone challenge. See Table 1 for abbreviations.

The possibility that the ventral tegmental area might play a role in the production of physical dependence is particularly important because this region has been shown to be involved in the rewarding action of opiates. Since the rostral periventricular gray site associated with maximal escape behavior was just two mm dorsal to the ventral tegmentum, we investigated the possibility that drug injected into the ventral tegmental area may have been diffusing up the cannula shaft and acting in the periventricular gray to produce physical dependence. Such drug efflux up the cannula shaft is a well-documented problem in intracranial injection studies (see Routtenberg, 1972). To test this possibility, we implanted another group of rats with cannulae aimed at the ventral tegmentum but angled to avoid penetration of the cerebral ventrical and lateral periventricular gray substance. As shown in Figure 1, rats with cannulae angled to avoid the periventricular gray region displayed little escape behavior during naloxone challenge.

Physical dependence as indexed by escape behavior thus seems to be produced by an action of morphine localized to the periventricular

gray region. The escape responding seen in animals receiving drug in the ventral tegmentum probably results from drug diffusion up the cannula shaft to the periventricular gray region. The results of this experiment, considered with the earlier localization of the reward-relevant opiate receptors in the ventral tegmentum (Bozarth & Wise, 1980, 1981a, 1982; Britt & Wise, 1981; Phillips & LePiane, 1980), suggest that the site of action for opiate reward and that for the production of physical dependence are anatomically dissociable. The demonstration that rats will work for morphine injected into the ventral tegmental area but not for morphine injected into the periventricular gray region (Bozarth & Wise, 1980, 1982) supports the notion that opiates can be rewarding because of a positive reinforcing action. This study does not, however, rule out the possibility that negative reinforcement mechanisms also contribute to the net rewarding effect during systemic delivery of opiates in which drug reaches both of these brain regions (see Weeks & Collins, 1979).

EXPERIMENT II: Temporal Dissociation of Reward & Physical Dependence

The intravenous self-administration paradigm has been used extensively to study the rewarding properties of abused drugs. Work with opiates has shown that laboratory animals will reliably self-administer opiates for prolonged periods of time and that physical dependence frequently accompanies this self-administration. Other self-administration studies have shown that animals will self-administer opiates at what appear to be sub-dependence producing doses (e.g., Woods & Schuster, 1968). Upon termination of testing, these subjects do not show obvious signs of physical dependence. Nonetheless, the failure to observe marked signs of abstinence does not eliminate the possibility that some degree of physical dependence has developed unnoticed in these subjects. The abstinence syndrome is accompanied by marked dysphoria in humans, and it is not clear that the autonomic effects that are usually quantified in animals are necessary for the production of this dysphoric response. It seems likely that some degree of withdrawal distress is produced by the termination of chronic opiate intake in animals and that this subjective state is not readily detectable with the current methods used by these investigators. Therefore, the relief of the withdrawal distress by subsequent opiate self-administration may not be ruled out as a factor in the control of opiate intake in any paradigm involving repeated drug administration.

To avoid the potentially confounding influence of negative reinforcement produced by the relief of withdrawal distress, we have assessed the rewarding impact of a single injection of heroin in rats. In a previous report, it was shown that animals which received a series of four heroin injections that were associated with a novel environment returned to the place where they had previously experienced the effects of these injections (Bozarth & Wise, 1981b). This conditioned place preference paradigm has been used to show the rewarding effects of several drugs including morphine (Rossi & Reid, 1976), heroin (Bozarth & Wise, 1981b), and

amphetamine (Sherman et al., 1980), and it has been proposed as a measure of the affective consequences of drug administration (Rossi & Reid, 1976). The present study involved testing for a conditioned place preference after only one injection of heroin, and thus there was no opportunity for the animals to learn about the effects of the drug injection on any opiate withdrawal discomfort.

Method

Naive rats were adapted to a shuttle box for five days and the amount of time spent on each side of the chamber was automatically recorded during 15 minute test sessions. One side of the test box had a plain plywood floor while the other side had a plywood floor covered with wire mesh. The amount of time spent on each of the two sides on the fifth trial was used to determine the initial place preference for each animal. On the sixth day, the rats were subcutaneously injected with heroin (0.5 mg/kg) or saline (1 ml/kg) immediately prior to being placed on their nonpreferred side of the shuttle box. A partition was used to confine the animals to their nonpreferred side for 30 minutes following the heroin injections. On the next day, the partition was removed and place preference was retested during a single 15-minute trial in the drug free state.

Results and Discussion

The single injection of heroin resulted in a significant shift in the animals' place preference suggesting that initial heroin administration is rewarding in these animals (see Figure 2). Since this study involved only one injection of drug, there was no opportunity for the drug injections to relieve withdrawal distress. Thus, positive reinforcement mechanisms are sufficient to account for the place preference of these animals.

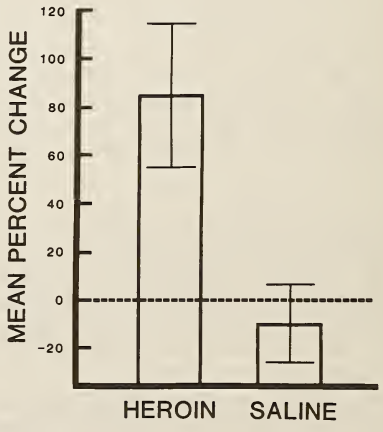

Figure 2: Mean (±SEM) percentage change in the amount of time spent on the non-preferred side of the test chamber following a single conditioning trial (n=12/group).

GENERAL DISCUSSION

Many theories of opiate addiction have focused on the physical dependence-producing properties of this class of drugs. The present studies show, however, that (i) the opiate receptor field mediating the physical dependence-producing effects of morphine is neuroanatomically dissociable from morphine's site of rewarding action (Experiment I) and (ii) the rewarding properties of heroin can be demonstrated at a time when there is no opportunity for the subjects to have developed an association between the drug injection and relief from withdrawal distress (Experiment II). Thus physical dependence is distinct from and not necessary for the positive reinforcing action of opiates.

The fact that opiates can serve as powerful positive reinforcers and that a state of physical dependence is not necessary for the rewarding properties to occur does not mean that the tendency to use the drug is independent of personality or psychosocial factors nor does it mean that physical dependence is irrelevant to the strength of the drug-taking habit. Indeed, it would seem likely that both positive and negative reinforcing effects make important contributions to governing the behavior of opiate addicts. The reported dissociation does, however, leave open the possibility that much of the rewarding impact of opiates is due to an action on the neural substrate involved in psychomotor stimulant and natural rewards (Wise & Bozarth, 1981)--an action which is independent of the physical dependence usually associated with opiate addiction.

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Buprenorphine Self-Administration by the Baboon: Comparison With Other Opioids

Scott E. Lukas, Roland R. Griffiths, and Joseph V. Brady

Animal drug self-administration procedures that have been developed and refined over the last two decades provide a great deal of information relevant to human drug-taking behavior. Numerous investigators, for example, have shown that animals will self-administer most drugs that are abused by humans (Griffiths et al., 1980; Johanson and Balster, 1978; Johanson and Schuster, 1981). In addition, a good correlation exists between the reported subjective effects of opioids and animal self-administration results (Griffiths and Balster, 1979).

The reinforcing properties of pure agonist opioids has been previously studied (Schuster and Woods, 1967; Deneau et al., 1969; Woods, 1980), but the recent development of opioids that possess both agonist and antagonist properties has provided a new and interesting sub-class of compounds that need to be evaluated.

The present study was undertaken to provide information on the relative reinforcing properties of a series of opioid mixed agonist/antagonist analgesics using a substitution drug self-administration procedure. Cocaine was used as the baseline drug in order to obviate potential problems associated with dependence development and, in addition, served as a reliable standard upon which the comparisons between opioids were made.

METHODS

Sixteen adult male baboons (Papio anubis) weighing 15-31 kg were subjects. Animals were adapted either to a standard restraint chair (Findley et al., 1971) or a harness-tether system (Lukas et al., 1982) and individually housed in a sound-attenuated chamber. Extraneous sounds were further masked by continuous white noise. Water via drinking tube was continuously available; animals also had the opportunity to respond for food (1 g Noyes monkey pellets) via a separate lever on a fixed ratio 30 schedule of reinforcement. Animals also received fresh fruit on a daily basis.

Each animal was surgically prepared with a jugular, femoral or

axillary venous catheter (inside diameter 0.79 mm, outside diameter, 2.36 mm), using the procedure described by Lukas et al. (1982). A detailed description of the drug injection system has been reported previously (Findley et al., 1972).

SELF-ADMINISTRATION PARADIGM

The availability of an injection was indicated by a 5-s tone and illumination of a light directly over a lever. Upon completion of a 160-response fixed-ratio requirement, the light over the lever was extinguished, the drug injection begun, and a 5 x 5 cm light was illuminated in the upper left-hand corner of the intelligence panel for a 1 hr period. A time-out period of 3 hr followed each injection, permitting a maximum of 8 injections per day. There was no time limit for completion of the fixed ratio response requirement.

Self-injection performance was first established with cocaine at a dose of 0.32 mg/kg. After three consecutive days of cocaine availability during which six or more injections were taken each day, a dose of test drug or vehicle was substituted for cocaine for a period of either 12 or 15 days. Cocaine was then reinstated, and when the criterion was met, another dose of a test drug was substituted. Drugs tested included codeine (0.01-10.0 mg/kg), butorphanol (0.00032-0.1 mg/kg), nalbuphine (0.001-0.1 mg/kg), pentazocine (0.01-10.0 mg/kg), buprenorphine (0.00032-1.0 mg/kg), d-,l- N-allyl normetazocine (SKF-10,047, 0.01-0.32 mg/kg), and naloxone (0.01-3.2 mg/kg).

RESULTS

Figure 1 depicts the self-administration pattern for various doses of codeine during the 15-day substitution period. When saline was substituted the number of daily self-injections quickly dropped from the 7-8 per day for cocaine (0.32 mg/kg/inj) to 1-2 per day. A similar profile was observed for the lowest dose of codeine. As the dose of codeine was increased, the number of daily self-injections increased (to 4-5 per day at the 0.32 mg/kg/inj dose, and to 7-8 per day at the 1.0 mg/kg/inj dose).

The results for the three mixed agonist/antagonist compounds butorphanol, nalbuphine, and pentazocine were similar to those for codeine. Butorphanol maintained self-injection behavior in the dose range of 0.001-0.1 mg/kg/inj while the reinforcing dose ranges for nalbuphine and pentazocine were 0.01-1.0 mg/kg/inj and 0.32-10.0 mg/kg/inj, respectively. In contrast, neither SKF-10,047 nor naloxone maintained performance above saline baseline levels over the dose range studied.

Self-administration of buprenorphine was characterized by only modest performance at the dose levels studied and appeared to reach a plateau in the 0.1-1.0 mg/kg/inj range (i.e., only 4-5 self-injections per day).

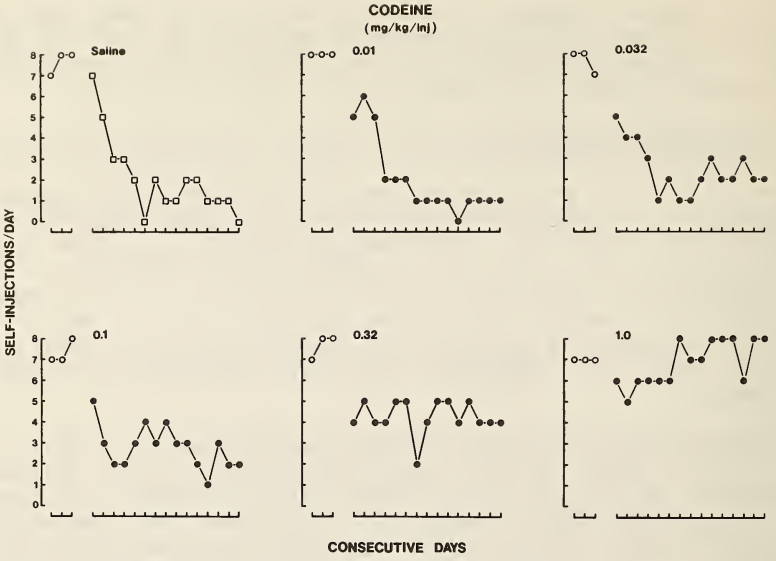

Figure 1. Self-injection of codeine during the 15-day substitution period in one subject. Open circles represent cocaine self-injections at a dose of 0.32 mg/kg.

When an ABA substitution procedure was employed in one animal, however, it was clear that buprenorphine did in fact serve as a reinforcer (figure 2). The 1.0 mg/kg/inj dose of buprenorphine maintained marginal self-injection behavior which quickly decreased after saline substitution. By the fourth day of buprenorphine re-substitution, the daily number of self-injections had returned to the pre-saline level.

DISCUSSION

The results of this study demonstrate clear differences among the seven compounds examined with respect to their maintenance of self-injection behavior. These findings replicate and extend previous studies of opioid self-administration in the non-human primate (Balster et al., 1977; Woods, 1977). Four of the opioids tested (codeine, butorphanol, nalbuphine, and pentazocine) maintained dose-related self-injection performance that was maximal (e.g., 7-8 injections per day) at some doses. Neither the racemic mixture of SKF-10,047 nor naloxone maintained performance above vehicle control.

In the present report, buprenorphine maintained only marginal rates of responding; although it clearly serves as a reinforcer as demonstrated by the saline substitution-resubstitution experiment (fig. 2). In addition, the dose-response curve appeared to reach a plateau at doses above 0.1 mg/kg/inj. These findings are in

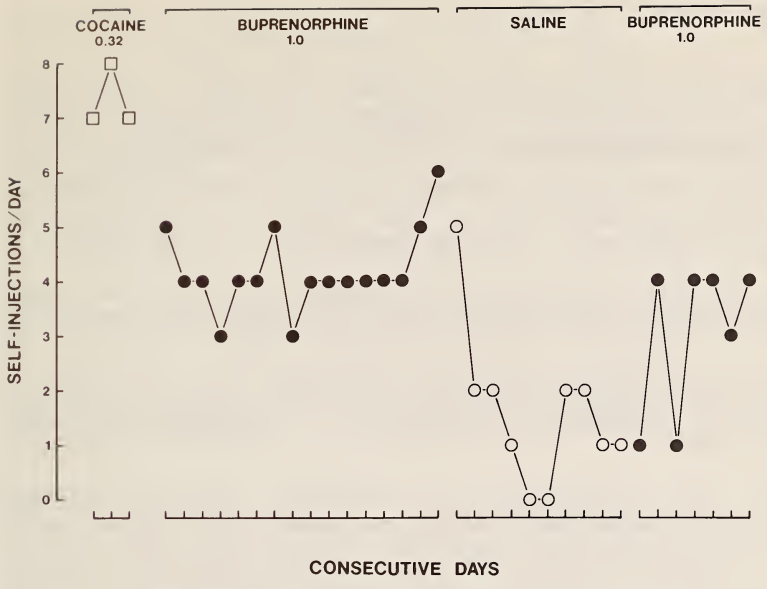

Figure 2. Self-injection of buprenorphine (1.0 mg/kg) after cocaine baseline and after saline extinction in one subject.

agreement with other reports. Woods (1977) compared buprenorphine with 32 other opioids using a substitution procedure (fixed ratio 30 schedule of reinforcement) and codeine as the baseline drug. Buprenorphine maintained response rates that were higher than saline-reinforced rates, but were only 54% of the rate maintained by codeine. No changes in the dose response curve were observed in the 0.003-0.1 mg/kg/inj dose range. Similar findings were reported by Mello et al. (1981) in which buprenorphine maintained responding on a second order schedule of reinforcement when substituted from a cocaine or a morphine baseline. The marginal reinforcing properties of buprenorphine were evident by the fact that only 3 out of 4 monkeys self-administered buprenorphine; only 1 of these 3 actually increased its intake with increasing doses. Finally, Yanagita et al. (1981) also demonstrated that buprenorphine possesses reinforcing properties that plateaued with higher doses and that performance was only 34-43% of the baseline drug, lefetamine (SPA).

In conclusion, the results of this study show that buprenorphine injections will maintain lever responding in baboons. When compared with other opioids, however, buprenorphine clearly maintains lower rates of responding and fewer daily injections. On the basis of the available data, no distinctions can be made between the reinforcing properties of codeine, butorphanol, nalbuphine and pentazocine, all of which maintained maximal performance.

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Somatic and Neurobiological Alterations in the Progeny of Female Rats Treated With Methadone Prior to Mating

Ian S. Zagon and Patricia J. McLaughlin

INTRODUCTION

Methadone, a synthetic narcotic analgesic, has received widespread use in detoxification and maintenance programs for heroin addicts, many of whom are females of childbearing age (Blinick et al. 1976). Clinical reports suggest that infants maternally exposed to methadone may be considered at risk for growth retardation and neurodevelopmental dysfunction (Wilson et al. 1973, 1979). Laboratory investigations support these clinical findings and demonstrate that animals exposed perinatally to methadone may suffer numerous difficulties including retarded somatic growth (McLaughlin et al. 1978; Zagon and McLaughlin 1977), neuroanatomical and neurochemical abnormalities (Zagon and McLaughlin 1978), physiological dysfunction (Rech et al.1980; Slotkin et al.1979; Thompson and Zagon 1981), alterations in nociception (Zagon and McLaughlin 1980), abnormal behavioral ontogeny (Zagon and McLaughlin 1978) and impaired learning ability (Zagon et al. 1979).

Given the problems in children of mothers treated with methadone, and since methadone is known to persist long after cessation of drug exposure (Harte et al. 1976), it is of great importance to determine whether women discontinuing consumption are in danger of bearing children who are physiologically and/or intellectually compromised. The present study was designed to address this question in a laboratory setting by examining the offspring of rats delivered by mothers who received daily injections of methadone for over 7 weeks and then were removed from drug treatment at least 1 week prior to mating. In addition to litter size and gestation time, infant mortality, birthweight, preweaning body, brain,and cerebellar growth, as well as nociception at 21 days served as criteria in our evaluation.

METHOD

Female (180-200 g) and male (400-450 g) Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) were used in this study. All animals were housed under controlled conditions (Zagon and McLaughlin 1978), with Purina Laboratory Chow and water available ad libitum. Ten female rats were randomly divided into groups of 5 rats each

and treated daily with an intraperitoneal injection of either 5 mg/kg dl-methadone hydrochloride (Dolophine, Eli Lilly Company, Indianapolis, IN) or 0.2 ml sterile saline. Animals were weighed every week and dosage adjustments made.

Five days after the beginning of drug treatment, the nulliparous females were placed with drug-free males for breeding. Females continued to receive drug injections daily throughout mating, gestation, and lactation. At weaning, the litters of offspring were removed from the female rats and used in other experiments. Drug treatment was terminated at this time and females were housed 5 per cage; all females were closely observed for signs of withdrawal (e.g., weight loss, tremors, wet-dog shakes). One week later, females previously exposed to methadone (M) or saline (C) were placed with drug-free males for breeding; the presence of sperm in vaginal smears indicated day 1 of pregnancy. On day 18 of gestation, females were placed in separate cages. At birth, litter size was noted and litters were culled to 8 pups per mother with an equal distribution of males and females. Animals were weighed on postnatal days 0, 10 and 21. At weaning (day 21), pups were tested for analgesia using an Analgesia Meter (Technilabs Instrument, Pequannock, NJ) at 55°C. Latency times were recorded (+ 0.1 sec) for each animal; pups were removed if no response occurred within 45 sec. Animals were then anesthetized with ether and fixed by cardiac perfusion with 10% neutral buffered formalin at an air pressure of 120 mm Hg. Brains were removed and placed in buffered formalin for 3 days before weights and measurements were made. Brain length was measured from a line extending from the rostral edge of the olfactory bulbs to the obex of the fourth ventricle. Cerebellar width was computed from a line extending parallel to the long folial axis. The brains (excluding olfactory bulbs) with cerebella were weighed; cerebella were then removed from the brainstem by transecting the peduncles as close to the cerebellum as possible, and weighed.

Body and brain weights and measurements, litter size, and analgesia scores were analyzed separately using analysis of variance; subsequent planned comparisons were made using Newman-Keuls procedure (Winer, 1971).

RESULTS

Females exposed to methadone prior to mating exhibited no difficulties in mating, conception, or parturition, and the length of gestation for these females was comparable to controls. Moreover, litter size and number of stillborns for animals in the M group ($\bar{x}$ = 14; n = 1, respectively) were similar to those of the C group ($\bar{x}$ = 12.7; n = 0, respectively). Examination of gross behavioral abnormalities associated with withdrawal were not recorded during mating, gestation or lactation in females of the M group, and the body weights of these animals during pregnancy resembled those of control females.

The birthweights (Table 1) of pups from mothers of the M group were reduced 20% from offspring of the C females. Body weights of pups in the M group were also lower than those from C females at 10 and 21 days, with reductions of 19% and 16%, respectively, noted.

TABLE 1

Body weights of offspring from mothers treated with methadone prior to mating

	AGE (days)		
	0	10	21
Control	7.52 ±0.36	23.82 ±0.74	47.52 ±1.79
Methadone	6.02** ±0.44	19.27* ±0.97	39.85** ±2.11

Values represent means ± S.E. for 12-33 pups per group at different ages. Significantly different from controls at $p<0.05$ (*) and $p<0.01$ (**).

TABLE 2

Brain and cerebellar weights and measurements of offspring from mothers treated with methadone prior to mating

	Brain Weight (g)	Brain Length (mm)	Cerebellar Weight (g)	Cerebellar Weight (mm)
Control	1.58 ±0.13	25.08 ±0.65	0.18 ±0.00	10.96 ±0.28
Methadone	1.37* ±0.12	23.87** ±0.11	0.18 ±0.01	11.15 ±0.09

Values represent means ± S.E. from 12-15 pups per group at 21 days of age. Significantly different from controls at $p<0.05$ (*) and $p<0.01$ (**).

Evaluation of brain weights and measurements (Table 2) at 21 days revealed that the brain weights of M pups were 87% control pups and the length of the brain was 95% of control rats. The cerebellum of M rats was comparable to control animals in both weight and width.

At 21 days, animals in the M and C groups were tested for nociceptive response. Pups in the M group were markedly ($p<0.01$) slower to react to the hot-plate than animals in the C group, with latency scores of the M pups (27.8 sec) being 2-fold greater than those for control rats (14.1 sec).

DISCUSSION

The results of the present study show that female rats chronically exposed to methadone prior to conception have offpsring with alterations in both somatic and neurobiological development. These offspring were lighter in weight than controls at birth and during

the preweaning period, and had brains that were subnormal in weight and length. Furthermore, rats delivered by mothers given a pregestational exposure to methadone were not as responsive to thermal stimuli in comparison to control animals. Interestingly, many of these deficits resemble those observed in rat offspring of mothers chronically receiving methadone during pregnancy and/or lactation (Zagon and McLaughlin, 1977, 1978, 1980).

Our observations confirm and extend the findings in other studies showing the effects of opioid consumption prior to mating. Friedler and colleagues have carried out several studies demonstrating that pregestational exposure of female rats (Friedler and Cochin, 1972) and mice (Friedler, 1978) to morphine results in growth retardation of offspring that can not be eliminated by cross-fostering. In some cases, F_2 generations were also affected in body weight and had pronounced movement deficits, indicating a cross-generational characteristic in effectiveness (Friedler, 1978). It also appears that opioid injections to male mice prior to mating may also be detrimental to subsequent progeny. Smith and Joffe (1975) have found an increased neonatal mortality in offspring of male rats given acute methadone or morphine treatments before mating, and Friedler and Wheeling (1979) have reported that male mice exposed to morphine prior to mating had offspring that exhibited behavioral alterations.

The mechanism underlying the disturbances in offspring of mothers treated with methadone prior to conception can only be speculated upon at this time. One possibility is that the process of drug withdrawal following long-term administration may serve to influence in utero development which may, in turn, have postnatal ramifications. However, evidence gathered in our study does not support this hypothesis. Overt signs of withdrawal such as tremors and wet-dog shakes were not observed during the period immediately following drug exposure nor during gestation or lactation. Moreover, body weight losses often encountered in animals undergoing abstinence were not found during the investigation. An alternative explanation may be that genetic alterations/mutagenicity could be involved in the course of methadone treatment, and that such factors could be imprinted on subsequent progeny. Although we have no evidence that would reflect on this hypothesis, it is known that opiates can damage chromosomes (Falek and Hollingsworth, 1980). Finally, it has been reported that methadone binds firmly to tissue proteins (Sung et al. 1953), and persists in several organs for up to 10 weeks after administration (Harte et al. 1976). In view of the absence of the blood-brain barrier in fetal and preweaning rats, and since immature organisms may not be able to cope with drugs as well as adults (Kandall, 1977), it certainly may be envisioned that any remaining methadone in the female rats could be effective in altering the course of fetal development. Regardless of the mechanism responsible, it does appear that the defects observed in offspring of mothers given methadone prior to mating may be of prenatal origin since the cerebellum, a part of the brain that undergoes extensive postnatal development, is unaffected in our experiment.

Differences in pharmacokinetics and routes of administration certainly make if difficult to make any direct comparisons between our

laboratory findings and the human situation. However, a number of parallels between laboratory and clinical studies, such as growth retardation and neurobehavioral disturbances, do suggest biological similarities in methadone's actions. In view of our findings and those of other investigators, it would seem prudent to assess the safety of bearing children following exposure to methadone or other opiates.

FOOTNOTES

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Differential Stereospecific Effects of Mu, Kappa, and Sigma Opioid Agonists on Cortical EEG Power Spectra in the Rat

Gerald A. Young and Naim Khazan

INTRODUCTION

We have recently reported that mu, kappa, and sigma opioid agonists produced differential effects on cortical EEG and EEG power spectra in the rat (Young et al. 1981). Intravenously administered morphine (mu agonist) produced high-voltage cortical EEG bursts associated with dose-related increases in EEG spectral power in the zero to 10 Hz band. Ketocyclazocine (kappa agonist) produced high-voltage cortical EEG bursts associated with dose-related increases in the 5 to 8 Hz band as a predominant spectral peak. N-allyl-normetazocine, SKF-10,047 (sigma agonist), produced desynchronized cortical EEG along with frequent theta wave activity, the EEG power spectra of which consisted of the minimal power peaking at about 7.5 Hz. These data further support the multiple receptor theories (Gilbert and Martin 1976; Lord et al. 1977; Martin et al. 1976) and complement the wide range of studies on opioid-receptor interactions (Chang et al. 1981; Wood et al. 1981). The pharmacological specificity of the differential effects of mu, kappa, and sigma opioid agonists on EEG and EEG power spectra was further assessed in the present study by delineating the effects of the enantiomers of each type of opioid agonist.

METHODS

Female Sprague-Dawley rats (250-300 g) were implanted with both bipolar epidural frontoparietal EEG electrodes and electromyographic (EMG) temporalis muscle electrodes and with indwelling jugular cannulae. For ipsilateral EEG recordings, stainless steel screws were implanted over the frontal (2 mm anterior and 2 mm lateral to bregma) and parietal (3 mm posterior and 2 mm lateral to bregma) cortices. Surgical procedures have been previously described (Khazan 1975). The intravenous cannulae were prepared and implanted according to the method of Weeks (1972).

During the experimental procedures, all rats were housed in individual chambers, 12" x 12" x 24". To permit unrestrained movement of the rat during EEG and EMG recordings, each cage was equipped with a swivel connector with concentric mercury pools which served as noise-free sliding contacts. A feed-through cannula for drug administration extended through the center of each swivel (Khazan et al. 1967). All rats were allowed to acclimatize to the experimental cages for two to three days before experimentation. Lighting conditions consisted of a timer-regulated lights-off period (10 p.m. - 6 a.m.).

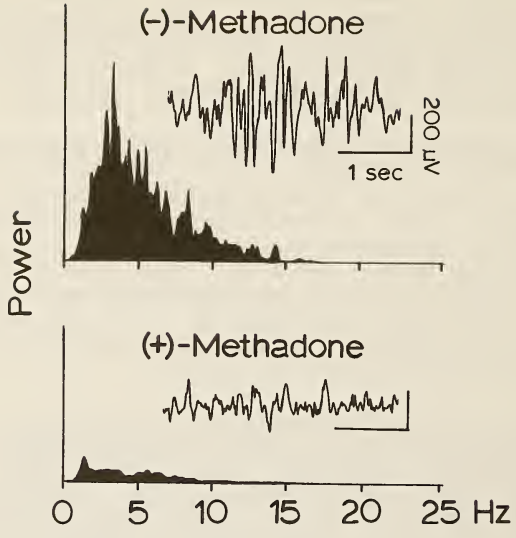
The enantiomers of methadone hydrochloride, ketocyclazocine methanesulfonate, and SKF-10,047 hydrochloride were administered in doses of 1.0, 1.25, and 2.5 mg/kg to three groups of three rats each, respectively. Both (-)- and (+)-methadone hydrochloride were dissolved in isotonic saline at a concentration of 1 mg/kg, and both (-)- and (+)-SKF-10,047 hydrochloride at a concentration of 10 mg/kg. Both (-)- and (+)-ketocyclazocine methanesulfonate were dissolved in a small amount of 0.5 N NaOH and brought up to a concentration of 2.5 mg/kg with isotonic saline. Injections of the appropriate vehicle on previous days served as the control.

For each rat, direct EEG and integrated EMG activities were continuously recorded on Grass polygraphs. EEG activities were filtered to pass frequencies between 1 and 35 Hz. EMG activities were filtered to pass frequencies between 10 and 75 Hz and were integrated. EEG activity was simultaneously recorded on FM tape using a Hewlett-Packard model 3960-A recorder. Power spectral analysis of the EEG was performed offline using a Nicolet MED-80 mini-computer system (Khazan and Young, 1980; Young et al, 1978a). For each rat and each opioid, EEG power spectra were derived from six separate 10-sec epochs of EEG that were digitized at a sampling rate of 100/sec, and power spectral densities were estimated at 0.05 Hz intervals from zero to 50 Hz. Average EEG power spectra were then obtained by averaging each of these sets of six spectra.

RESULTS

Representative cortical EEG samples and associated EEG power spectra following intravenous administration of (-)-methadone and (+)-methadone (1 mg/kg) are shown in Figure 1. (-)-Methadone injection produced high-voltage EEG bursts superimposed on a background of desynchronized EEG activity. Behaviorally, (-)-methadone-induced high-voltage EEG bursts were associated with stupor or catalepsy, exophthalmos, and respiratory depression. These EEG and behavioral effects of (-)-methadone continued for one-half to one hour following the injection of 1 mg/kg. Associated cortical EEG power spectra consisted of predominant power in the zero to 10 Hz range. These effects of the (-) enantiomer of methadone were similar to those produced by the racemic mixture of either morphine or methadone. In contrast, the (+) enantiomer of methadone did not induce behavioral change; the EEG and EEG power spectra were analogous to those of normal wakefulness.

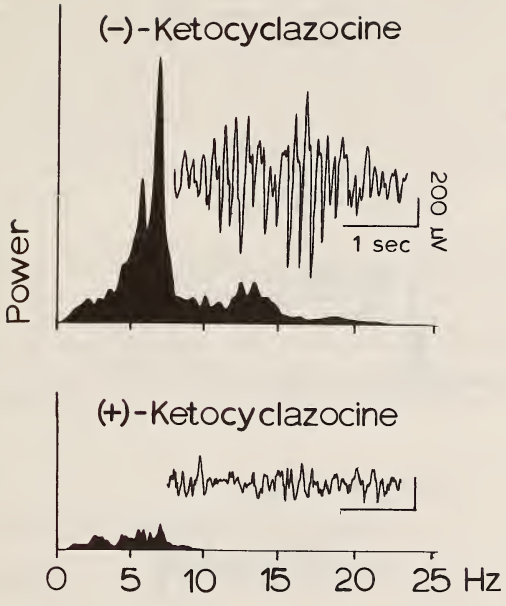
FIGURE 1



Cortical EEG recordings and related power spectra after acute intravenous administration of (-) and (+)-methadone (1.0 mg/kg) in an individual rat.

(-)-Ketocyclazocine injection also produced high-voltage EEG bursts (Figure 2). However, the high voltage EEG bursts produced by (-)-ketocyclazocine consisted of more regular, sinusoidal-like waveforms than those produced by morphine. Additionally, the (-)-ketocyclazocine-induced high-voltage EEG bursts occurred on a background of considerable theta wave activity, in contrast to a desynchronized EEG background activity following methadone or morphine administration. Behaviorally, (-)-ketocyclazocine-induced high-voltage EEG bursts were associated with stupor or catalepsy, exophthalmos, and respiratory depression that were as a whole similar to the behavioral effect produced by methadone or morphine. These EEG and behavioral effects of (-)-ketocyclazocine lasted for one-half to one hour after the 1.25 mg/kg dose. Associated EEG power spectra had a prominent peak in the 5-8 Hz band. (-)-Ketocyclazocine produced effects similar to those produced by the racemic mixture. Conversely, (+)-ketocyclazocine induced neither EEG nor behavioral changes. Both the EEG and EEG power spectra were those of normal wakefulness.

FIGURE 2

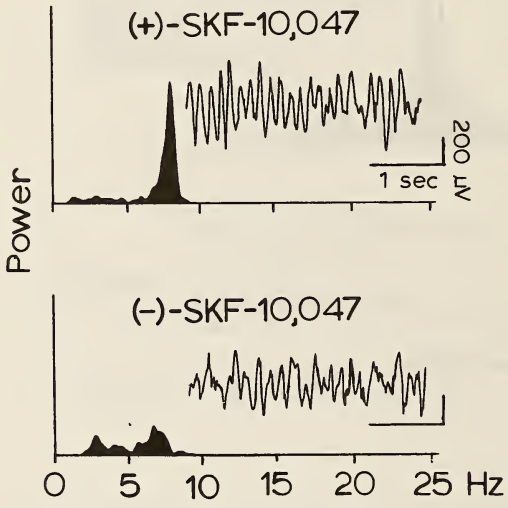


Cortical EEG recordings and related power spectra after acute intravenous administration of (-)- and (+)-ketocyclazocine (1.25 mg/kg) in an individual rat.

As shown in Figure 3, (+)-SKF-10,047 produced long EEG episodes of theta wave activity. The associated power spectra had a prominent peak in the 7-9 Hz band. Behaviorally, (+)-SKF-10,047 produced circling, erect ears, moderate exophthalmos, episodes of backing up and "piano playing" with the front paws, abortive grooming, and mild ataxia. These EEG and behavioral effects produced by 2.5 mg/kg of (+)-SKF-10,047 continued for 10 to 20 minutes. A mixture of EEG theta waves and desynchronized waveforms were produced by (-)-SKF-10,047. The associated EEG power spectra reflected aroused wakefulness, similar to those produced by the racemic mixture. Behaviorally, (-)-SKF-10,047 produced ataxia, crawling, or crouched walking, frequent periods of stillness (rats were responsive to stimulation), and moderate exophthalmos. These EEG and behavioral effects produced by (-)-SKF-10,047 continued for 20 to 40 minutes following administration of 2.5 mg/kg. The racemic mixture of SKF-10,047 produced desynchronized EEG waveforms that were associated with frequent occurrences of theta wave activity,

similar to (-)-SKF-10,047. However, in contrast to either (+)- or (-)-SKF-10,047, rats were behaviorally aroused with prolonged periods of stereotypic activities such as chewing and licking. This EEG and behavioral effect of the racemic mixture of SKF-10,047 persisted for one-half to one hour following the 5 mg/kg dose.

FIGURE 3



Cortical EEG recordings and related power spectra after acute intravenous administration of (+)- and (-)-SKF-10,047 (2.5 mg/kg) in an individual rat.

DISCUSSION

Stereospecific effects of the enantiomers of methadone, ketocyclazocine, and SKF-10,047 were delineated. While both (-) enantiomers of methadone and ketocyclazocine were active, the (+) enantiomers were not. The (+) enantiomer of SKF-10,047 induced behavioral changes that were reminiscent of the behavioral effects produced by a psychomimetic agent like dimethyl- or diethyltryptamine (Siegel et al. 1974). Thus, our findings lend further support to the theories of multiple opioid receptors (Gilbert and Martin 1976; Lord et al. 1977; Martin et al. 1976) and complement the recent biochemical findings (Chang et al. 1981; Wood et al. 1981).

We have previously characterized qualitative and quantitative differences in cortical EEG power spectra associated with the behavioral states of SWS, rapid eye movement (REM) sleep, and wakefulness in the rat (Young et al. 1978a). When one compares the EEG power spectra associated with opioid administration in the present study with the EEG power spectra previously shown to be associated with the above three behavioral states, it is apparent that the EEG power spectra produced by morphine and ketocyclazocine are several times higher in total density area than the EEG power spectra associated with any of the behavioral states of either SWS, REM sleep, or wakefulness. The EEG power spectra associated with SKF-10,047 administration (racemic mixture) represents an aroused state of behavior.

Utilizing the EEG spectral analysis, we have previously studied and reported on the CNS effects of several narcotic agonists, antagonists, and mixed agonist-antagonists (Kareti et al. 1980; Lukas et al. 1980; Steinfels et al. 1980; Young et al. 1978b, 1981), ethanol (Wolf et al. 1981), and Δ^9-tetrahydrocannabinol (Buonamici et al. 1982). The present study offers additional characterization of the enantiomers of selective μ, κ, and σ opioid agonists.

REFERENCES

References will be furnished upon request.

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Relationship Between Reinforcing Properties and Sensory/Motor Toxicity of CNS Depressants; Implications for the Assessment of Abuse Liability

Joseph V. Brady, Scott E. Lukas, and Robert D. Hienz

INTRODUCTION

Preclinical assessment procedures developed over the past two decades for evaluating drug dependence potential and abuse liability have demonstrated a good correspondence between the compounds self-administered by laboratory animals and those abused by humans (Deneau et al., 1969; Griffiths et al., 1976, 1980, 1981; Schuster and Thompson, 1969). The proper evaluation of drugs from a broader abuse liability perspective, however, would seem to require an assessment of the relationship between these reinforcing effects and the disruptive pharmacological/behavioral effects of such compounds. Substances with only minimal (if any) disruptive behavioral or pharmacological activity are not generally regarded as having significant abuse liability even though self-administration may be widespread (e.g., caffeine in tea or coffee). In contrast, compounds used even sparingly which produce disruptive pharmacological/behavioral changes are considered to have high abuse liability (e.g., lysergic acid diethylamide). Drugs may fall anywhere on the continua defined by these parameters, and the present report describes a quantitative approach to the comparative evaluation of drugs based upon this relationship.

More specifically, a "reinforcement/toxicity ratio" is proposed for comparing the relative potency of a drug as a reinforcer maintaining self-administration, on the one hand, with its relative potency as regards disruptive effects upon sensory and motor functions, on the other. A drug with potent reinforcing properties (i.e., maintains self-injection at relatively low doses) but which produces disruptive effects only at relatively high doses would have a low reinforcement/toxicity ratio, whereas a drug which maintains self-injection only at relatively high doses but produces disruptive sensory/motor effects at relatively low doses would have a high reinforcement/toxicity ratio. The measure thus provides a potentially useful preclinical assessment of the extent to which self-administration of a compound may disrupt basic sensory/motor processes as well.

METHODS AND PROCEDURES

The reinforcing properties of three barbiturates (amobarbital, pentobarbital, secobarbital) and two dissociative anesthetics (ketamine and phencyclidine) were evaluated with 10 laboratory baboons to determine the dose of each compound which maintained criterion self-administration. The procedure for determining reinforcing properties has been previously described in detail (Griffiths et al., 1976, 1981) and involved the initial establishment of drug self-administration with cocaine (0.32 mg/kg/injection) followed by substitution of saline or another drug dose for cocaine. Amobarbital (0.1-17.8 mg/kg), pentobarbital (0.1-17.8 mg/kg), secobarbital (0.1-17.8 mg/kg), ketamine (0.01-1.0 mg/kg), and phencyclidine (0.01-1.0 mg/kg) were studied under conditions which required completion of a fixed number of responses on a lever (i.e., a 160-response fixed-ratio schedule) for intravenous injections. A 3-hour time-out period followed each injection, permitting a maximum of eight injections per day. When saline or low doses of drugs were substituted, the number of injections taken decreased over successive days. When higher doses of the drugs were substituted for cocaine, however, the self-injection rate was reliably maintained above saline control levels. Figure 1, for example, shows the effects of dose on the number of pentobarbital injections per day self-administered by two of the baboon subjects in the study, and illustrates the procedure used for determining the criterion reinforcing dose values.

All drugs were also evaluated to determine the criterion dose which produced a 50% change in auditory and/or visual thresholds, and/or a 10% change in motor reaction time. The procedures for determining such sensory/motor toxicity have been previously described in detail (Brady et al., 1979; Hienz and Brady, 1981; Hienz et al., 1981) and involved training baboons to press and hold a lever until presentation of a sound burst or light flash signalled availability of food reward contingent upon lever release (i.e., reaction time paradigm). During auditory testing, 16.0 kHz pure tones were delivered through an overhead wide-range acoustic speaker located 20 cm above ear level. During visual testing, a circular white patch at eye level on the response panel was illuminated at different intensities. Trials started with a dimly flashing red cue light that became steady contiguous with a lever press, and thus served as feedback for the lever holding response. At varying intervals (1.0 to 7.3 sec.) following initiation of the holding response, a test stimulus (1.5 sec. duration) was presented. Release of the lever in the presence of the test stimulus defined a correct detection of the stimulus, and produced a food pellet reward, terminated the test stimulus, and initiated a 1-sec intertrial interval (ITI). Lever releases prior to test stimulus onset or following test stimulus offset reinstated the ITI without food delivery. Reappearance of the flashing red cue light following the 1-sec ITI signalled initiation of the next trial. Daily 2 to 2.5 hour experimental sessions were conducted in a double-walled sound-attenuating chamber, and included approximately 700 such discrete reaction time trials.

Auditory and visual thresholds were determined in separate sessions by randomly varying the intensity of the test stimuli from trial-to-trial in accordance with the method of constant stimuli, and

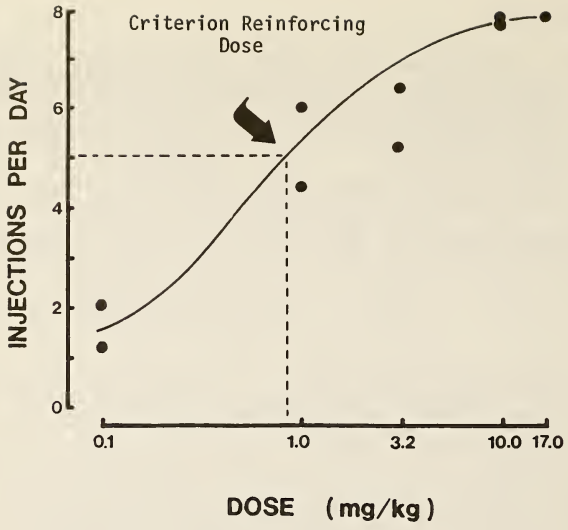

Figure 1. Daily pentobarbital self-injections as a function of dose. The criterion dose for self-administration (dotted line) was halfway between the performance maintained by saline (i.e., 1-2 inj/day) and maximal performance on cocaine (i.e., 7-8 inj/day).

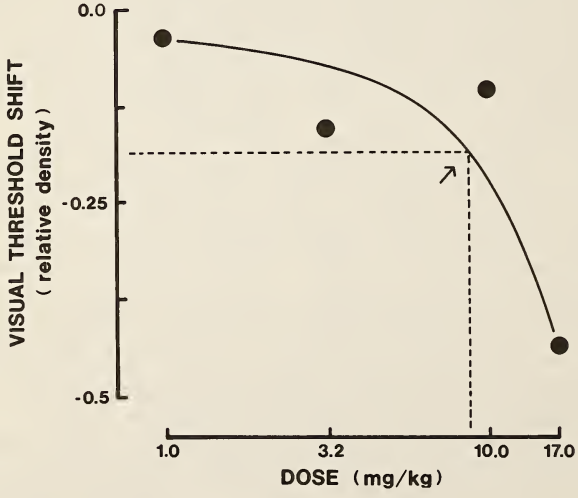

Figure 2. Visual threshold shift as a function of pentobarbital dose. Values are the means of three baboons. The criterion sensory threshold toxicity dose (dotted line) was halfway between central and maximal change.

examining detection frequencies at each intensity. For the auditory modality, four intensity levels 10 dB apart of a 16.0 kHz tone were used, with the lowest level set just below an animal's estimated threshold. For the visual modality, four intensity levels of the white light were used, 0.5 log density units apart, with the lowest level set just below the animal's threshold. False-alarm rates were also measured by occasionally presenting "no-stimulus" trials. Reaction times were measured as elapsed time between signal onset and lever release. Drugs were administered intramuscularly (i.m.) immediately before each experimental session, followed by 15 minutes of dark adaptation and 15 minutes of "warm-up" on the reaction time task before threshold determinations were begun. Saline control sessions requiring return-to-baseline performances occurred between drug sessions. Figure 2 shows an example of the effects of pentobarbital dose level upon visual threshold in three baboons and illustrates the determination of toxic dose values.

RESULTS

All three barbiturates and both dissociative anesthetics (Table 1, Column A) maintained drug self-administration rates as a function of dose level, and the criterion dose of each compound which maintained intravenous self-injection is shown in Table 1, Column B. Dose-dependent increases in reaction time were also observed with all five drugs, and the dose of each compound which produced the criterion 10% change in this measure is shown in Table 1, Column C. The resulting Reinforcement/Reaction-Time-Toxicity Ratios derived from the relationship between the criterion reinforcing dose (i.e., Column B, numerator) and the reaction time toxicity dose (i.e., Column C, denominator) are shown in Table 1, Column D for each of the five drugs studied. The ratio values range from a low of 0.07 for amobarbital to a high of 1.22 for phencyclidine.

Dose-dependent increases in sensory thresholds were also observed with all five drugs, and the criterion dose of each compound which produced a 50% change in either auditory or visual threshold is shown in Table 1, Column E. The resulting Reinforcement/Sensory-Threshold-Toxicity Ratios derived from the relationship between criterion reinforcing dose (i.e., Column B, numerator) and the sensory threshold toxicity dose (Column E, denominator) are shown in Table 1, Column F for each of the five drugs studied. The ratio values range from a low of 0.04 for amobarbital to a high of 2.0 for phencyclidine.

Table 1: Reinforcement/Toxicity Ratios for three barbiturates and two dissociative anesthetics. Determination of doses is described in text. The criterion reinforcing doses in Column B were derived by multiplying the actual doses by a constant that corrects for differential absorption rates and makes the I.V. self-administration doses more comparable to the I.M. toxicity doses.

A	B	C	D	E	F
Drug	Criterion Reinforcing Dose (mg/kg)	Criterion Reaction-Time Toxicity Dose (mg/kg)	Reinforcement/ Reaction-Time Toxicity Ratio (B/C)	Criterion Sensory-Threshold-Toxicity Dose (mg/kg)	Reinforcement/ Sensory Threshold Toxicity Ratio (B/E)
Phencyclidine	0.05	0.041	1.22	0.025	2.00
Ketamine	0.39	1.20	0.33	0.40	0.98
Secobarbital	1.80	3.30	0.55	6.60	0.27
Pentobarbital	1.44	4.78	0.30	9.60	0.15
Amobarbital	0.44	5.90	0.07	11.60	0.04

Figure 3 summarizes in graphic form the relationship between the criterion sensory and motor change doses and the criterion self-administration dose for the five compounds thus far studied. With the broken diagonal line representing equality between the reinforcing and the toxic doses, all three barbiturates are seen to cluster above the diagonal (upper right corner), indicating that the doses which produce disruptive sensory/motor changes are generally higher than the doses required to maintain self-administration of these compounds. Moreover, there is a consistent relationship between the sensory and motor effects of these three barbiturates, with the motor effects appearing at lower doses than the sensory effects. In contrast, both ketamine and phencyclidine are readily differentiated from the three barbiturates by the consistent appearance of sensory changes at doses below those which produce motor effects. The phencyclidine values can also be seen to fall below the diagonal (lower left corner), indicating that the doses required to maintain self-administration are generally higher than the doses which produce disruptive sensory/motor changes.

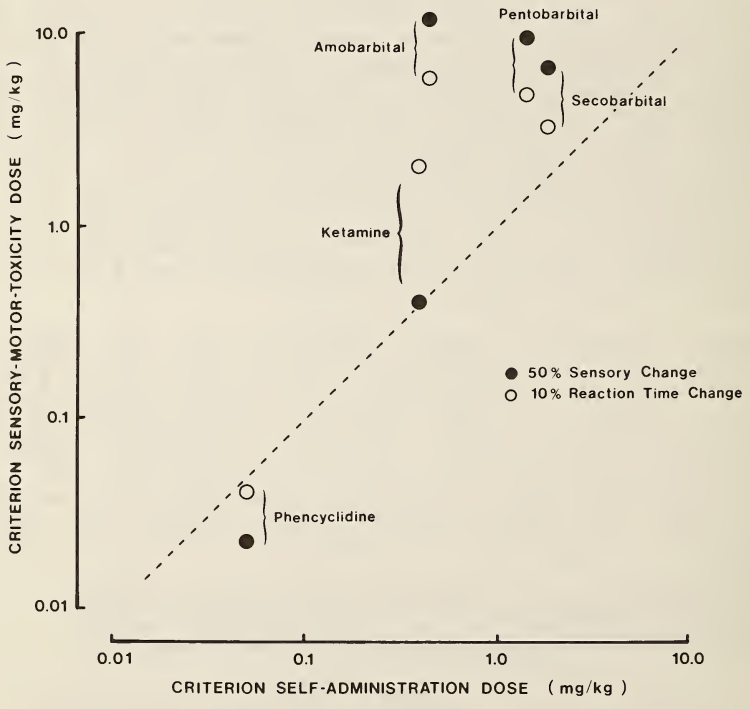

Figure 3. Relationship between criterion sensory and motor toxicity doses and criterion self-administration doses for three barbiturates and two dissociative anesthetics. The broken diagonal line represents equality between the reinforcing and toxic doses.

DISCUSSION

The ordering of compounds derived from analyzing the relationship between reinforcing efficacy and behavioral toxicity shows that there are wide ranging differences between drugs of abuse, with the Reinforcement/Toxicity Ratios for phencyclidine being up to 20-50 times greater than those for amobarbital. The high ratio values reflect the fact that such compounds have disruptive sensory/motor effects at lower doses (relative to their reinforcing potency) than compounds with lower ratios. And in the case of phencyclidine, these behaviorally toxic effects can occur below the reinforcing dose (Fig. 3). In contrast, the low ratio values reflect the fact that a drug has disruptive sensory/motor effects at higher doses (relative to its reinforcing efficacy) than compounds with higher ratios. Amobarbital, for example, maintained self-administration at doses below those which produce behaviorally toxic effects (Fig. 3).

The sensory toxicity dose values for the compounds included in the present report were determined on the basis of criterion changes in either auditory or visual thresholds as a first approximation in analyzing their relationships to reinforcing potency. That these compounds can produce differential effects as a function of sensory modality and drug dose has been convincingly documented in recent studies of the psychophysical profiles of drugs of abuse (Brady et al., 1979; Hienz and Brady, 1981; Hienz et al., 1981). The results of these latter experiments have shown, for example, that the barbiturates can produce significant elevations in the visual threshold at doses which produce no change in the auditory threshold. These findings suggest that the relationships described in the present report can be extended to provide a much more specific analysis of the nature and degree of disruptive effects under various conditions of drug self-administration.

Drug self-administration procedures with laboratory animals have provided an important conceptual and methodological focus for the preclinical assessment of pharmacological agents. Extending drug evaluations to include analysis of the relationship between these reinforcing effects and the behavioral/pharmacological effects of a compound adds a critical dimension to the assessment of its abuse liability. Caution is required however when, as in the present report, estimates of reinforcing efficacy and behavioral toxicity are derived under circumstances which limit the range of species variations, drug dosing schedules, routes of administration, as well as a host of other historical influences both environmental and pharmacological. The Reinforcement/Toxicity Ratio, based upon the relationship between such determinations of reinforcing potency on the one hand, and sensory/motor toxicity on the other, may nonetheless add a useful and important quantitative dimension to the preclinical assessment of drug abuse liability.

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Diazepam, Pentobarbital, and Methaqualone Effects on Several Behaviors in the Rat and Antagonism by Ro 15-1788

David J. Mokler and Richard H. Rech

The sedative hypnotics may exert their effects through a number of different mechanisms. Diazepam interacts with a specific receptor linked to a GABA receptor and a Cl^- ionophore (Skolnick and Paul, 1981) and enhances the binding affinity of the GABA receptor for its ligand. Barbiturates may act at an additional receptor linked to this complex (Olsen, 1981). The sites of action of methaqualone have yet to be defined.

Recently Hunkeler et al. (1981) synthesized a new class of compounds, the imidazodiazepines, the prototype being Ro 15-1788. They showed that Ro 15-1788 inhibits ^{3}H-diazepam binding to brain synaptosomes, reverses diazepam-induced protection against metrazol seizures, and alleviates the disruption induced by diazepam in a horizontal wire test. Ro 15-1788 does not affect the depression induced by phenobarbital, meprobamate or ethanol. In a standard conflict paradigm Ro 15-1788 prevents the antipunishment effect of diazepam. Ro 15-1788 also antagonizes the decrease in rat cerebellar cGMP by diazepam, but not that by barbiturates, ethanol or meprobamate (Mohler et al., 1981), and reverses the effects of 3-methylclonazepam in a number of tests in humans (Darragh et al., 1981).

We have investigated the effects of diazepam (DZ), pentobarbital (PB) and methaqualone (MQ) alone and in combination with Ro 15-1788 in a novel conflict paradigm, conditioned suppression of drinking (CSD), as well as in rotarod performance (RR) and motor activity (MA).

METHODS

Conditioned Suppression of Drinking (CSD). Female Sprague-Dawley rats (150-200 g; Spartan Research Animals, Inc., Haslett, MI) were water-deprived and trained to drink in 10 min daily sessions from a tube protruding through the wall of a 30x56x28 cm plexiglass cage with stainless steel floor (Kilts et al., 1981). The drinking tube was attached to a calibrated (±0.5 ml) polyethylene tube to monitor fluid consumption. When drinking had stabilized, 7-sec tones were presented on a variable interval 21 sec schedule. During the last 5 sec of the tone the drinking tube and cage floor were electrified (0.03 mA current, C.J. Applegate,

Stimulator Model No. 250, Boulder, CO). Animals were tested six days a week at the same time of day.

Drug treatments were administered every 3-4 days. DZ, PB and MQ were administered 10 min and Ro 15-1788 immediately before the session. The number of shocks received (punished responding) and the volume of water consumed (unpunished responding) on 'drug-days' were divided by these measures for the day immediately prior to obtain percent of control shocks taken and water consumed, respectively. Changes in water or shocks were compared using a multi-factorial ANOVA with least significant differences for multiple comparisons; $p<0.05$ was used as the criterion for statistical significance.

Rotarod Performance (RR). Female Sprague-Dawley rats were trained to walk on a rotating rod (RR, 8 rpm). Drugs were tested after animals had reached criterion of walking 180 sec for two consecutive trials on two consecutive days. Thirty mg/kg DZ, 18 mg/kg PB, 18 mg/kg MQ, or saline was administered 15 min before testing and 2.0 mg/kg Ro 15-1788 or saline was administered 5 min before testing. Animals were then placed on the RR for two consecutive trials; the longest walk was recorded. Mean scores for each drug were compared using a one-way ANOVA with least significant differences for multiple comparisons ($p < 0.05$ = level of significance).

Motor Activity (MA). Rats used previously in a RR experiment were randomly divided into groups regardless of previous drug experience. Animals were given 18 mg/kg DZ, 18 mg/kg PB, 18 mg/kg MQ or saline 15 min before and 2 mg/kg Ro 15-1788 or saline 5 min before being placed into motor activity cages. Total counts over 15 minutes were recorded using a Stoelting electromagnetic-field counter. Statistical analysis was done as described for RR performance.

Drugs. All drugs were administered i.p. and doses were randomized. Ro 15-1788 and DZ were gifts from Hoffman-LaRoche, Inc (Nutley, NJ). PB sodium was obtained from Sigma Chemical Co. (St. Louis, MO). MQ free base was a gift from Wm. H. Rorer, Inc. (Fort Washington, PA). Ro 15-1788, DZ and MQ were suspended in 0.5% methylcellulose with two drops/10 ml Tween 80. PB sodium was dissolved in distilled water.

RESULTS

CSD. Baseline responding consisted of 15.5 ± 0.5 (mean $\pm$ S.E.M., n = 20) ml of water consumed per session and 17 ± 2 (mean $\pm$ S.E.M., n = 20) shocks taken. Both measures were stable across control sessions. Ro 15-1788 (0.5, 1 or 2 mg/kg), administered alone immediately before the sessions, did not alter shock or water scores (zero dose, Fig. 1). DZ (3, 5.6, 10, 18 and 30 mg/kg) caused a significant increase in punished responding (shocks) and, at doses of 18 and 30 mg/kg, caused a decrease in unpunished responding (water intake). Ro 15-1788 caused a dose-dependent attenuation of the effects of DZ on punished responding ($F(3, 182) = 21.4$).

At a dose of 0.5 mg/kg, Ro 15-1788 in combination with DZ significantly reduced the DZ anticonflict effect, although shocks taken were still above baseline with several dose levels. Water intake, reduced by 18 mg/kg DZ

was significantly different from DZ alone after the drug combination. The 1.0 mg/kg dose of Ro 15-1788 nullified the DZ anticonflict effect for all but the 18 mg/kg dose; the DZ-induced decrease in water intake was reversed by the combination at the 30 mg/kg DZ dose level but not at 18 mg/kg DZ. At 2.0 mg/kg, Ro 15-1788 combined with DZ resulted in complete attenuation of the DZ anticonflict effect. The reduction of water intake by DZ was not reversed by combination with 2.0 mg/kg Ro 15-1788.

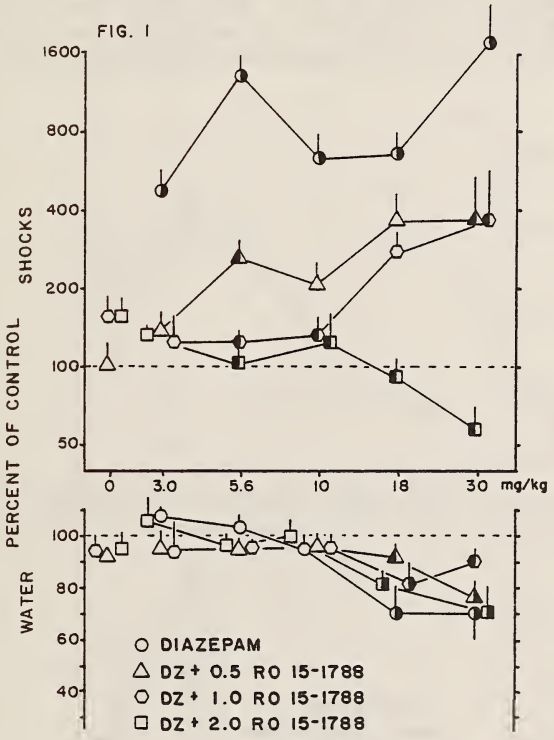

FIG. 1. Effects of diazepam alone and in combination with Ro 15-1788 in CSD. ◑ = significantly different from control, ◭ = significantly different from diazepam alone, $p<0.05$.

PB (3 to 18 mg/kg) also released punished responding (Fig. 2), being maximal at 10 mg/kg. Water intake was significantly decreased at 10 and 18 mg/kg PB. Combination with 1 or 2 mg/kg Ro 15-1788 did not alter the PB effect on the punished component of this behavior. Unpunished behavior, however, was significantly potentiated at 18 mg/kg PB by combination with 1 or 2 mg/kg Ro 15-1788. MQ (5.6 to 30 mg/kg) also caused a release of punished responding, increasing shocks at 10, 18 and 30 mg/kg (Fig. 3). Unpunished responding was decreased by MQ alone at doses of 18 and 30 mg/kg. Combination with Ro 15-1788 (1 mg/kg) did not alter the effects of MQ on either punished or unpunished responding.

RR. The results of RR experiments are seen in Fig. 4. Ro 15-1788 (2 mg/kg) did not alter RR performance. DZ (30 mg/kg) caused a significant

disruption of performance; this effect was reversed by Ro 15-1788 combined with 30 mg/kg DZ. In contrast, the disruption by 18 mg/kg PB was significantly potentiated by combining with Ro 15-1788. Ro 15-1788 had no effect on the disruption of RR walking by 18 mg/kg MQ.

MA. When compared to saline controls, 2 mg/kg Ro 15-1788 did not have an effect by itself on MA measured over 15 min (Fig. 5). DZ (18 mg/kg) caused a significant reduction in MA which was almost completely reversed by combination with Ro 15-1788. When Ro 15-1788 was given to animals receiving either 18 mg/kg PB or 18 mg/kg MQ, their MA was not significantly different from that of animals receiving the same dose of PB or MQ alone.

FIG. 2

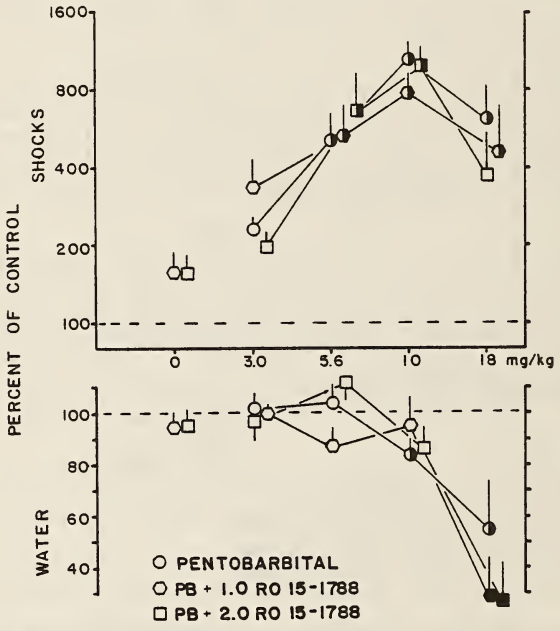

FIG. 2. Effects of pentobarbital alone and in combination with Ro 15-1788 in CSD. ◑ = significantly different from control, ◧ = significantly different from pentobarbital alone, $p<0.05$.

DISCUSSION

In agreement with Kilts et al. (1981) DZ caused a release of punished responding in this conditioned suppression paradigm. Only at higher doses (18 and 30 mg/kg) were depressant effects of DZ observed on water intake. Since water intake is insignificant during tone periods, it serves as a good measure of unpunished responding in the CSD. For example, 5.6 mg/kg DZ increased punished responding by 1400% without altering the level of intake from control (Fig. 1).

Ro 15-1788 caused a dose-dependent attenuation of the release of punished responding elicited by DZ. However, Ro 15-1788 may not

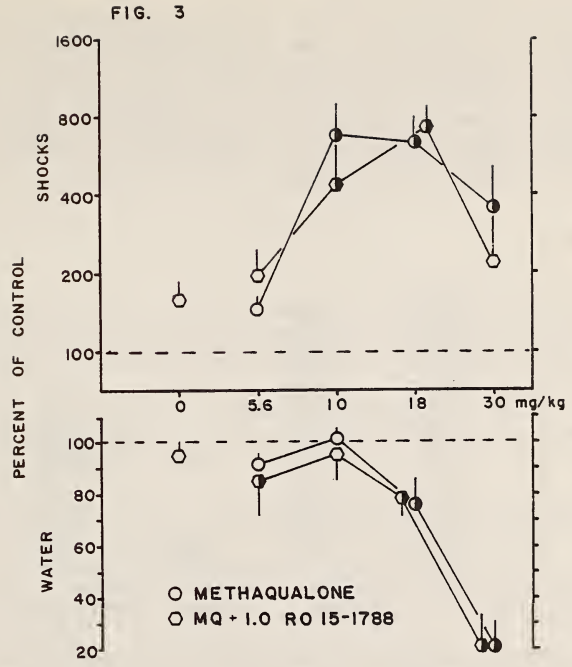

FIG. 3. Effects of methaqualone alone and in combination with Ro 15-1788 in CSD. ◑ = significantly different from control, $p<0.05$.

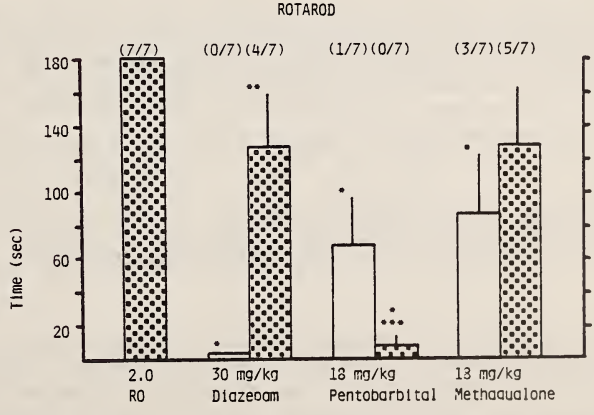

FIG. 4. Effects of diazepam, pentobarbital and methaqualone alone (open bars) or in combination with 2.0 mg/kg Ro 15-1788 (filled bars) on rotarod performance. * = significantly different from Ro 15-1788 alone, ** = significantly different from diazepam alone, *** = significantly different from pentobarbital alone, $p<0.05$.

antagonize some depressant effects of DZ, as evidenced by the inability of Ro 15-1788 to reverse in a clear dose-dependent manner the decrease in unpunished responding after higher doses of DZ. This is in contrast to the findings of Darragh et al. (1981) that Ro 15-1788 is capable of reversing the depressant side effects of 3-methylclonazepam in humans. It may be that higher doses of Ro 15-1788 would be capable of reversing these depressant effects in the CSD.

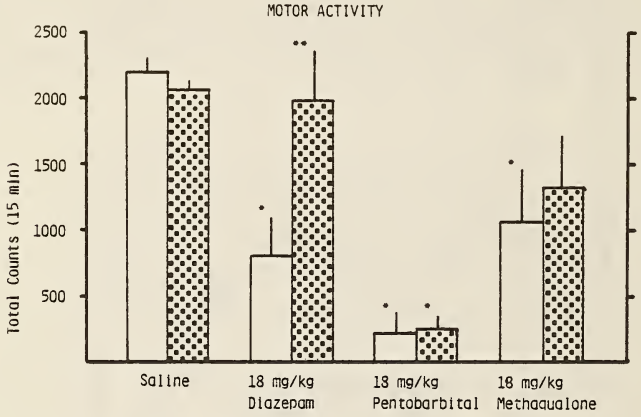

FIG. 5. Effects of diazepam, pentobarbital and methaqualone alone (open bars) or in combination with 2.0 mg/kg Ro 15-1788 (filled bars) on motor activity. * = significantly different from saline alone, ** = significantly different from diazepam alone, $p<0.05$.

The apparent lack of effect of Ro 15-1788 on the release of punishment-suppressed behavior by PB would suggest that the anti-anxiety effects of PB are not related to a specific benzodiazepine effect, in agreement with other investigators, Barrett and Brady (1982), Brady (this volume), and Gorodetzky (this volume). The potentiation by Ro 15-1788 of the depression in water consumption by higher doses of PB may indicate some interaction between these two drugs, however. This has also been suggested by Barrett and Brady (1982): Ro 15-1788 potentiated the effects of PB in another conflict test. Ro 15-1788 also did not reverse the anti-conflict effects of MQ, suggesting that this compound is similar to PB in not interacting with the benzodiazepine receptor to produce its effects.

Ro 15-1788 reversed the disruptive effects of DZ on RR and MA, a paradox when contrasted with the lack of a clear-cut antagonism by Ro 15-1788 of the DZ decrease in the unpunished component of the CSD. This suggests that these depressant actions may be working through different mechanisms. The potentiation by Ro 15-1788 of PB disruption of RR further supports an interaction between these drugs. The current study has not ruled out pharmacokinetic interaction. The lack of effect of Ro 15-1788 on MQ disruption of RR and MA suggests that this drug works by mechanisms that differ from both DZ and PB.

These experiments indicate that these examples of the sedative-hypnotic class of drugs exert their effects through a number of different mecha-

nisms. The anticonflict effects of DZ are clearly mediated through a mechanism which is antagonized by Ro 15-1788. This may not be the case for the decrease in water intake by DZ in the CSD paradigm. The anticonflict effects of PB and MQ, however, are clearly not mediated through a Ro 15-1788-blockable mechanism. The effects of Ro 15-1788 on RR and MA depressant actions of DZ, PB and MQ further separate these drugs as to mechanisms. Obviously, further study of these interactions is desirable to further define differences in the mechanisms of action of these sedative-hypnotic agents.

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Alcohol Effects on Estradiol in Female Macaque Monkey

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The effects of alcohol on male reproductive function have been studied extensively. Impotence, testicular atrophy, gynecomastia and loss of sexual interest are often associated with alcoholism. Both acute and chronic alcohol intoxication significantly suppress plasma testosterone levels in normal men (Gordon et al. 1976; Mendelson et al. 1977), alcoholics (Mendelson and Mello, 1974) and rodents (Badr and Bartke, 1974; Cicero and Badger, 1977). Testicular, prostatic and seminal vesicle atrophy have been reported in rodents (cf. Cicero, 1980a & b).

In alcoholic women, there is clinical evidence of menstrual and procreative dysfunction including amenorrhea, infertility, menstrual irregularities (Bourne and Light, 1979; Hugues et al, 1980), and spontaneous abortions (Harlap and Shiono, 1980). However, there has been a surprising lack of systematic studies of the effects of alcohol on female reproductive hormones. It is not known whether alcohol interferes with female reproductive function at the level of the ovaries or the hypothalamic-pituitary axis (cf. Cicero, 1980b).

This report describes the first evaluation of the acute effects of alcohol on neuroendocrine hormones essential for reproductive function in the female macaque monkey. Patterns of neuroendocrine hormone secretion during the menstrual cycle are similar in rhesus monkey and women. The rhesus monkey has been the preferred model for reproductive physiologists for decades (Knobil, 1980).

METHODS

The acute effects of alcohol on 17-β estradiol, luteinizing hormone and follicle stimulating hormone were studied at four phases of the menstrual cycle (menstruation, ovulation, mid-luteal phase and the pre-menstruum). Progesterone was also studied at the mid-luteal phase. Alcohol at doses of 1.5, 2.5, and 3.5 g/kg were compared with equal volume isocaloric control solutions. This

range of alcohol doses produced peak blood alcohol levels between 150 and 325 mg/dl. Data are reported for the primary female reproductive hormone 17-β estradiol, which is analogous to testosterone in the male. Analysis of the other hormones is still in progress.

Sexually mature macaque monkeys (6 M. mulatta, 1 M. nemestrina) (4.0 to 8.5 kg) were acquired from commercial suppliers, quarantined and housed individually in a cage room with adult male rhesus monkeys. All females were alcohol and drug naive except one that had a brief history of alcohol self-administration, but had been alcohol free for 95 days at the initiation of these studies.

Monkeys were maintained on food and water ad lib. Monkey chow was supplemented with fresh fruit, vegetables and multiple vitamins. Daily vaginal swabs were taken to determine the onset and duration of menstruation. A 12-hour light-dark cycle (7 a.m. to 7 p.m.) was in effect.

When each monkey's menstrual cycle became stable (after two to six months), acute doses of alcohol were given to coincide with menstruation and the predicted time of ovulation, the mid-luteal period, and the pre-menstruum. The accuracy of predictions of each menstrual cycle phase could not be established until the onset of the next menses. Ovulation was later confirmed by radioimmunoassay of estradiol. It was seldom feasible to study the acute effects of alcohol at each of the four menstrual cycle phases during a single menstrual cycle. Consequently, it was necessary to follow the monkeys over 12 to 18 consecutive menstrual cycles in order to evaluate the effects of three doses of alcohol and isocaloric control solutions at four verified menstrual cycle phases.

Alcohol (1.5, 2.5, and 3.5 g/kg) was prepared in a 25% solution (v/v) and administered through a pediatric grade nasogastric tube. Monkeys were fasted for 18 hours to insure uniform absorption of alcohol from the small intestine.

Since gonadal steroids and pituitary gonadotropins are secreted episodically (Knobil, 1980; Yen, 1980), we devised a procedure for integrated blood sample collections (Bree et al, 1982). Integrated plasma samples were exfused continuously over four or five hours and aliquots were collected every thirty minutes. Each sample reflected the true mean level of each hormone measured for that thirty-minute period, whereas a bolus sample might coincide with the peak or nadir of episodic secretory activity. A full description of the integrated plasma sample collection procedure has been published (Bree et al. 1982).

Plasma levels of 17-β estradiol were determined in duplicate by radioimmunoassay using a modification of the procedure of Hotchkiss et al. (1971). After diethyl ether extraction, estradiol was measured directly without chromatography. Goat anti-rabbit

gamma-globulin, rather than dextran-coated charcoal, was used to separate the bound from the free steroid. Antiserum to 17-β estradiol (No. 26-47, Endocrine Sciences, Tarzana, CA.) was essentially free of cross reactivity to other estrogens and known plasma steroids; the greatest cross reactivity (1.3%) was with estrone. The labeled steroid used for the assay was the radioiodinated (125_I) 7-succinyl tyrosine methyl ester derivitive of 17-β estradiol (Cat. No. D-1240 Micromedics Systems, Horsham, PA.). 17-β estradiol (2, 4, 6, 7, 16, 17-^{3}H) (Cat. No. NET-517, New England Nuclear, Boston, MA.) was used for extraction recovery corrections. Intra- and inter-assay C.V.s were 6% and 19%.

Levels of alcohol in blood were measured in duplicate, in plasma samples, by a colorometric, micromethod (Léric et al, 1970). This method is based on oxidation of ethanol to acid aldehyde catalyzed by yeast alcohol dehydrogenase, with nicotinamide adenine dinucleotide (NAD) as co-factor. The NADH produced reacts with p-iodonitrotetrazolium violet (INT) and phenozine methylsulphate (PMS) to form a formazan dye that absorbs at 500 nm.

RESULTS AND DISCUSSION

The time-course and range of blood alcohol levels achieved after doses of 1.5, 2.5, and 3.5 g/kg are shown in Figure 1. At lower alcohol doses, peak blood alcohol levels were above 125 mg/dl, which is a high level of intoxication in a non-alcoholic person. The legal limit of intoxication in most states is 100 mg/dl. At the highest alcohol dose (3.5 g/kg) peak blood alcohol levels exceeded 300 mg/dl, a level sometimes seen in chronic alcoholic individuals. Monkeys appeared severely intoxicated at 2.5 and 3.5 g/kg alcohol doses. Since respiratory failure and death can occur at blood alcohol levels of 450 to 600 mg/dl, we did not risk administering higher doses of alcohol.

There was no correlation between plasma estradiol levels and the ascending and peak blood alcohol levels. Moreover, estradiol levels did not decrease as a function of increasing doses of alcohol at any phase of the menstrual cycle. Comparison of each post-alcohol sample with the pre-alcohol sample for the group of monkeys showed no statistically significant differences. Comparison of each post-alcohol sample with the post-sucrose samples for the group of monkeys also showed no statistically significant differences.

Figure 2 shows the percent change in estradiol from the sucrose control levels after each dose of alcohol. These findings illustrate the lack of alcohol dose-related changes in estradiol during menstruation. Blood samples for hormone analysis were collected on the first, second or third day of menstruation as determined by vaginal swabs. Comparable findings were obtained during the premenstruum (1, 2, or 3 days immediately before the onset of menstruation).

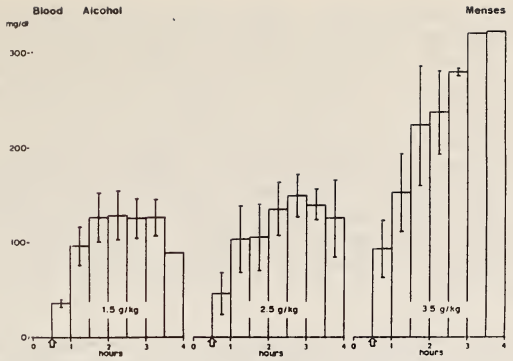

Fig. 1. Average blood alcohol levels during the ascending and peak phase of the blood alcohol curve, after nasogastric intubation of 1.5, 2.5 and 3.5 g/kg alcohol.

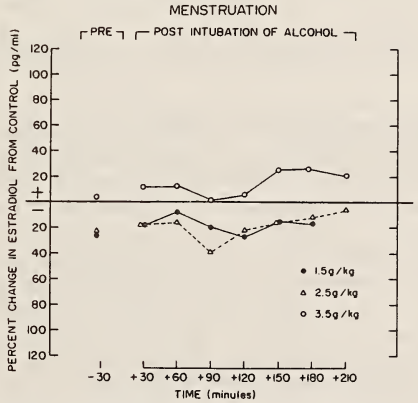

Fig. 2. Acute alcohol effects on 17-β estradiol. Each point represents an average of six monkeys.

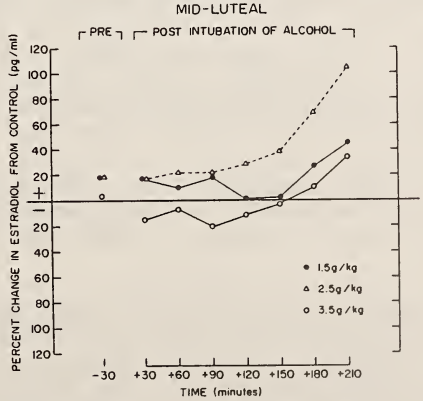

Fig. 3. Acute alcohol effects on 17-β estradiol. Data following 1.5 and 2.5 g/kg alcohol represent an average of five monkeys. Data following 3.5 g/kg alcohol represents an average of four monkeys.

Normally, estradiol levels are lowest during menstruation and the pre-menstruum so that an alcohol-induced suppression might be difficult to detect. Estradiol levels are highest during ovulation and therefore might be most sensitive to an alcohol-related suppression. Unfortunately, accurate prediction of ovulation proved to be extremely difficult. Estimates that appeared valid (15 to 17 days before the onset of menstruation) were not always confirmed by radioimmunoassay. Eighteen of twenty-five sample collection days were not confirmed as ovulation using the criterion that estradiol levels must exceed 200 pg/ml. There were no alcohol dose-related changes in estradiol during ovulation in the seven valid sample days.

The only statistically significant changes in estradiol following acute alcohol administration occurred during the mid-luteal phase after 2.5 g/kg of alcohol. Figure 3 shows the percent change in estradiol from sucrose control levels. Estradiol levels were significantly elevated at 150, 180 and 210 minutes after alcohol ($p < .05$ to .01). However, no significant changes in estradiol followed administration of a higher dose of alcohol (3.5 g/kg).

It was anticipated that acute doses of alcohol would produce a decrement in estradiol comparable to that seen in the male hormone, testosterone. In human males, acute doses of alcohol sufficient to produce peak blood alcohol levels of 109 mg/dl resulted in a significant dose-dependent decrease in plasma testosterone (Mendelson et al, 1977). Single doses of alcohol have consistently resulted in dose-dependent decreases in plasma testosterone in rodents (see Cicero, 1980a & b). It was surprising to find that even very high doses of alcohol, sufficient to produce blood alcohol levels above 300 mg/dl, did not suppress estradiol in females, since estradiol production requires essentially the same biosynthetic pathways as testosterone production in males.

In order to insure that the absence of acute alcohol effects on estradiol in rhesus monkey females did not reflect some heretofore unrecognized species difference, control studies of the acute effects of alcohol (2.5 and 3.5 g/kg) were conducted in male macaque monkeys. Preliminary findings from on-going studies have shown a highly significant alcohol dose-related decrement in male macaque plasma testosterone levels. Pre-alcohol control values averaging between 1000 and 1400 ng/dl fell to 200 to 300 ng/dl within 210 minutes after acute alcohol administration. These data suggest that alcohol effects on testosterone in rhesus males are comparable to those consistently observed in other species (Cicero, 1980a & b).

The lack of alcohol effects on estradiol in female macaque monkeys is consistent with our recent study of the effects of a single low dose of alcohol on estradiol, luteinizing hormone and prolactin in human females (Mendelson et al, 1981). Low doses of alcohol sufficient to produce peak blood alcohol levels of 88 mg/dl had no significant effect on estradiol in comparison to isocaloric sucrose solutions in six women. These women were studied at only

one phase of their menstrual cycle, the mid-follicular phase, 8, 9 or 10 days following menstruation. These data suggest that there may be a differential vulnerability to the acute effects of alcohol on reproductive hormones in males and females.

However, most clinical reports of menstrual aberrations associated with alcohol have occurred in chronic alcoholic women. We are currently studying the effects of chronic high dose alcohol administration on reproductive hormones and menstrual cycle regularity in a behavioral (alcohol self-administration) paradigm and a forced alcohol administration paradigm. Studies in progress indicate that chronic alcohol administration at levels of 4 gm/kg/day and above disrupt menstrual cycle regularity and suppress ovulation. Parametric studies to determine the time-course and alcohol dose range over which effects comparable to those observed in alcoholic women may occur in monkey are in progress.

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Modulation of Phencyclidine Receptor Sensitivity

Remi Quirion and Candace B. Pert

INTRODUCTION

In the past decade, phencyclidine (PCP) has become a major drug of abuse in the United States (1). Because of its unique pharmacological profile which bears some resemblence to schizophrenia (2), a great deal of research on possible mechanisms of action of PCP have recently been published (1,2). One of the most interesting possibilities is the existence of a specific receptor for PCP in brain. Zukin and Zukin (3) and Vincent et al. (4) have provided evidence for the presence of such PCP receptors in rat brain. Using the brain slice technique, we have confirmed these results (5,6), and showed that the autoradiographic distribution of PCP binding sites in rat brain are unique (5,6), being mainly concentrated in the hippocampus and cortex. These PCP binding sites appear to be stereoselective (7). Interestingly, benzomorphan, which possesses "σ" pharmacological effects (8), are the only class of opiates which interact with the PCP receptor (5,6,9,10).

In this paper, we provide further characterization of PCP binding sites. First of all, we described the action of the two isomers of N-Allylnormetazocine (SKF 10,047, a σ-opiate agonist) on these binding sites. We also reported the effect of amantadine, an antiviral compound with anti-Parkinsonian activity (11) on the same sites. Finally, we reported the effect of a chronic PCP treatment on various receptors such as PCP receptors, dopamine receptors and opiate receptors. Because of the apparent plasticity of PCP binding sites, these results strenghtened our hypothesis that these sites represent the biological substrate on which PCP acts to induce its multiple actions.

MATERIALS AND METHODS

Rat olfactory bulb slices were prepared as described before (5). Frozen slide-mounted sections were preincubated for 15 min in 5.0 mM Tris-HCl, 50 mM sucrose, 20 mM NaCl, pH 7.4 at 0°C, followed by a 45-min incubation in the same buffer (without NaCl), pH 7.4 at

0°C with 8.2 nM [^{3}H]-PCP (48 Ci/mmol; New England Nuclear), in the presence of various concentrations (+) SKF 10,047 or (-) SKF 10,047 and amantadine or its inactive analogue, rimantadine. At the end of the incubation, the slides were transferred sequentially through six rinses (30 sec in each) of 5.0 mM Tris-HCl buffer plus 50 mM sucrose, pH 7.4 at 0°C plus 1% bovine serum albumin. Binding of [^{3}H]-PCP to the tissue slice was quantitated by counting the tissue-laden slide fragment in 10 ml Aquassure scintillation cocktail (New England Nuclear). Specific binding was calculated as the difference in counts bound in the presence and absence of 0.1 mM PCP.

For chronic PCP treatment, male Sprague-Dawley rats weighing 250-310 g (from Zivic-Miller Laboratories, Inc., Allison Park, PA) received a daily subcutaneous injection of 10 mg/kg PCP in saline or saline alone (controls) for 14 consecutive days. Animals were sacrificed on day 15 and their brains were rapidly immersed in sopentane at -40°C, mounted on cryostat chucks and olfactory bulbs (for PCP binding) and striatum (for dopamine and opiate binding) were cut into 25 µm-thick coronal sections at -14°C. Sections were thaw-mounted on gelatin-coated slides, air-dried on ice for 2 hr, and then stored at -14°C for at least 48 hr before use. For PCP, frozen olfactory bulb slide-mounted sections were preincubated and incubated as described above, with various concentrations of [^{3}H]-PCP. For the opiate binding study, striatum slide-mounted sections were incubated for 30 min in 50 mM Tris-HCl, 3 mM Mn $(OAc)_2$, pH 7.4 at 25°C with various concentrations of [^{3}H]-dihydromorphine (73 Ci/mmol; Amersham, DHM). For the dopamine binding study, striatum slide-mounted sections were incubated for 30 min in 50 mM Tris-HCl, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 3 mM Mn $(OAc)_2$, 0.1% ascorbic acid, 50 nM ketanserin with pH 7.4 at 25°C, with various concentrations of [^{3}H]-spiperone (27.6 Ci/mmol; New England Nuclear). At the end of the incubation period, the slides were washed in cold buffer as described above for [^{3}H]-PCP. For [^{3}H]-DHM, the slides were transferred sequentially through six rinses (20 sec in each of the cold buffers) (12). For [^{3}H]-spiperone, the slides were transferred through six rinses (1 min in each) of cold incubation buffer and then dipped in and out of distilled water to remove ions. Under these conditions, specific [^{3}H]-spiperone binding represents 70-75% of total binding (Quirion and Pert, in preparation). Binding of [^{3}H]-PCP, [^{3}H]-DHM and [^{3}H]-spiperone to the tissue slide were quantitated by assaying the tissue bearing slide fragment in 10 ml of aquassure scintillation cocktail. Specific binding was calculated as the difference in counts bound in presence and absence of 0.1 mM PCP for [^{3}H]-PCP binding, 1.0 µM etorphine for [^{3}H]-DHM binding and 1.0 µM (+)- butaclamol for [^{3}H]-spiperone binding. Scatchard analysis of the binding data was used for calculation of receptor concentration (B_{max}) and dissociation constant (K_D). The means of the calculated values (B_{max} and K_D) for control and treated rats were compared for significant differences by the Student's t-test.

TABLE 1
RELATIVE POTENCIES OF STEREOISOMERS OF N-ALLYLNORMETAZOCINE (SKF 10,047) on [^{3}H]PCP BINDING

COMPOUND	IC_{50}, nM	Relative Potency
PCP	90 + 9.0	1.0
(±) SKF 10,047	300 + 40	0.30
(+) SKF 10,047	280 + 50	0.32
(-) SKF 10,047	3200 + 400*	0.03

*$p < 0.001$; $n = 3$

Table 1 shows that (+) SKF 10,047 is a least ten times more potent than (-) SKF 10,047 in displacing [^{3}H]-PCP from its binding sites. In fact, since (+) SKF 10,047 is as potent as (±) SKF 10,047, it is likely that (+) SKF 10,047 represents the active isomer of the mixture. Recently, Brady *et al.* (13) have also reported that in monkeys trained to discriminate between saline and PCP or PCP-like compounds, only (+) SKF 10,047 was recognized as a PCP-like drug. (-) SKF 10,047 was totally inactive in the same test. Thus, it appears that first the (+) isomer of σ-like benzomorphans are able to interact with PCP, and the (-) isomer being active on opiate receptors (13). These results may explain some of the conflicting results obtained with a mixture of isomers of various benzomorphans (e.g., cyclazocine).

TABLE 2
EFFECTS OF AMANTADINE OF [^{3}H]-PCP BINDING

DRUG	[^{3}H]-PCP K_D (nM)	[^{3}H]-PCP B_{max} (fmole/slice)
Control	52 ± 4.0	10.6 ± 0.9
Amantadine (10 nM)	41 ± 3.0*	11.0 ± 0.8
Amantadine (100 nM)	36 ± 3.0**	9.9 ± 0.7
Rimantadine (100 nM)	54 ± 5.0	11.4 ± 1.0

Numbers are mean ± SEM of three determinations each in triplicate.
* $p < 0.05$
** $p < 0.01$

Amantadine is an antiviral drug which has been shown, unexpectedly, to improve the symptomatic condition of parkinsonian patients (11). The mechanism of action related to this antiparkinsonism activity is not completely understood, but appears to be due to the dopamine-releasing properties of amantadine (14-15). As shown in Table 2, amantadine significantly increases the affinity (Kd) of [^{3}H]-PCP for its binding site in a dose dependent manner. The number of sites (B_{max}) does not appear to be changed by the presence of amantadine in the incubation buffer. Interestingly enough, rimantadine, an analogue of amantadine with antiviral properties, but completely devoid of any central nervous system effects, is also totally inactive on the [^{3}H]-PCP binding site.

It is tempting to speculate that maybe some of the CNS effects of amantadine are related to an action of this drug on the PCP receptor complex. It is well known that PCP is able to induce the release of dopamine in various conditions (16) and acts as a "non-amphetamine" stimulant of the dopaminergic system (17). Since the mechanisms of action of amantadine appears to involve the release of dopamine from the pre-synaptic areas(14-15), it is possible that both amantadine and PCP act on the same substrate to induce the release of dopamine in the brain. Also, this interaction of amantadine on the PCP binding site may explain some of the CNS effects of this antiviral drug. In fact, it had been reported that both PCP (1) and amantadine (18) induced hallucinations in humans.

TABLE 3
EFFECTS OF CHRONIC PCP TREATMENT ON PCP, OPIATE AND DOPAMINE BINDING PARAMETERS IN RAT BRAIN SLICES

LIGAND	K_D (nM)		B_{max} (fmol/slice)	
	Control	Treated	Control	Treated
^{3}H-PCP	44 ± 5(1)	52 ± 5	11.4 ± 0.9	7.6 ± 0.6 (2)
^{3}H-Spiperone	0.54± 0.05	0.62± 0.04	38.0 ± 2.1	26.0 ± 1.9 (3)
^{3}-DHM	1.3 ± 0.2	1.5 ± 0.2	47.2 ± 3.7	45.1 ± 3.6

(1)Values represent mean ± SEM of 3 experiments, each in triplicate.
(2)$p < 0.01$
(3)$p < 0.005$

Finally, a chronic PCP treatment caused a significant decrease in the number (B_{max}) of [^{3}H]-PCP and [^{3}H]-spiperone binding sites in rat brain slices (Table 3). For [^{3}H]-PCP, we observed a 33% decrease in the number of sites and for [^{3}H]-spiperone, the B_{max} is 31% lower in treated than in control rats (Table 3). No changes in the affinity (K_D) of the receptors for [^{3}H]-PCP and [^{3}H]-spiperone were observed (Table 3). Also, [^{3}H]-DHM binding was not affected (B_{max} and K_D) by a chronic PCP treatment (Table 3).

Our results show that a chronic PCP treatment induced a decrease in number of [^{3}H]-PCP binding sites in rat brain. Much evidence suggest that there is an inverse relationship between the number of receptors and the degree of receptor occupancy by agonists. PCP receptors also appear to be regulated that way. This down-regulation of the number of PCP sites induced by chronic PCP treatment may explain the development of tolerance (19,20) and dependence (21) to this drug observed in various species.

The diminution in the number of [^{3}H]-spiperone binding sites, an antagonist of the D-2 dopamine receptor after chronic PCP treatment is interesting, especially in regard to the "schizophrenic-like" effects induced by PCP. Since a direct interaction of PCP on dopamine binding sites in unlikely (22), the decrease in D-2 binding sites in rat striatum might be related to the various effects of PCP on the dopaminergic system (23). Since it has been shown that PCP can induce the release of dopamine in various preparations (17), it is possible that some PCP binding sites might be located on dopaminergic terminals and can stimulate the release of dopamine, which in a chronic situation induces a down-regulation of the number of D-2 dopamine binding sites. Another explanation might be that PCP can block the uptake of dopamine (16,17), thus inducing a decrease in the number of binding sites because of the higher than normal concentration of dopamine in the synaptic cleft. In any case, the diminution of D-2 dopamine binding sites may contribute in some way to the development of tolerance and dependence to PCP.

The absence of effect of chronic PCP treatment on opiate binding sites indicates that there is little cross-reactivity between opiates and PCP. It has already been shown that very high concentrations of PCP are necessary to inhibit opiate binding *in vitro* (24). However, some benzomorphans with a peculiar "σ" opiate effects appear to be the only class of opiates which possess strong interaction with PCP-like drugs (5,6,9,10).

In conclusion, our results demonstrate further that only opiate-like compounds are able to interact with PCP receptors. Moreover, amantadine, which represents a totally different class of drugs, also interacts with the PCP binding site. Finally, a chronic PCP treatment appears to decrease the number of PCP receptors in rat brain, which may provide some explanation for the development of tolerance and dependence to PCP. This plasticity of the PCP receptor complex provides evidence that [^{3}H]-PCP binding sites represent the functional PCP receptor.

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Ciramadol (Wy-15,705) and Codeine Analgesia After Episiotomy

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Ciramadol (Fig 1) is one of a new series of analgesics known as mixed narcotic agonist-antagonists. In animal models (unpublished data) onset of analgesia was rapid, within 15 to 30 minutes, and duration was 3 to 5 hours. Effects on vital centers were minimal, and ciramadol neither substituted for morphine in acute studies nor produced direct dependence when administered chronically to monkeys. These characteristics, combined with a low incidence of side effects of a mild nature in humans (Camu, 1981; Staquet, 1980), give ciramadol the potential to fill a gap in the spectrum of available drugs for the relief of pain. Early studies in humans demonstrated single doses to be safe when administered intramuscularly and orally at doses up to 20 and 60 mg, respectively (unpublished data). Oral ciramadol is rapidly absorbed with peak plasma levels occurring within 1 to 2 hours, and the half-life is 3 to 6 hours. Urinary excretion is the primary

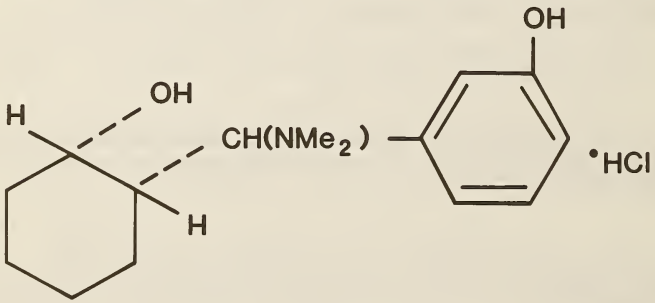

Fig 1 Ciramadol (Wy-15,705),1-cis-2-(α-dimethylamino-m-hydroxybenzyl) cyclohexanol-HCl

elimination pathway for ciramadol and its major conjugated metabolite (unpublished data). In previous double-blind and open clinical studies the types of pain treated orally included post-operative, postepisiotomy and pain due to malignancy. Postoperative pain was also treated parenterally. In general, moderate to severe pain responded to oral doses of 20 to 60 mg. However, the minimum effective oral dose was not clearly demonstrated. Adverse effects were infrequently encountered and consisted primarily of nausea, vomiting and/or dizziness. In single doses, sedation was not reported; however, in a multiple dose study, mild sedation did occur (Cochrane, 1979). There were no abnormal laboratory parameters or electrocardiographic findings due to the drug reported after single doses of ciramadol (unpublished data). The present report is of a late phase II investigation to clarify minimum and optimum effective analgesic doses of ciramadol when administered in single oral doses. It was performed in hospitalized women with moderate or severe pain after episiotomy (Bloomfield et al. 1976).

METHODS

The experimental protocol was the usual one used for oral studies in our clinical analgesic program. Subjects included in this report were a homogeneous population of 157 consecutive healthy consenting hospitalized postpartum women 18 years of age or older complaining of moderate or severe postepisiotomy pain within 24 hours of an uncomplicated delivery. This study included only episiotomy pain; afterbirth cramping pain was not measured. Also excluded were patients who were breastfeeding their infants, those given analgesics or other CNS drugs within the previous 3 hours, and those with a history of a known hypersensitivity to narcotics or narcotic antagonists. On enrollment, patients were stratified according to their initial pain intensity, moderate or severe. Those with only mild pain were not included.

The design included a concurrent comparison of 5 experimental treatments: 3 graded dose levels of ciramadol, 15 mg, 30 mg, and 60 mg, one dose level, 60 mg, of codeine sulfate, and placebo. All experimental medications were in the form of identical coded tablets, administered on demand as a single oral dose of one tablet with 8 oz of water. Patients were instructed to lie on their right sides for 2 hours after administration.

Treatment allocation involved parallel groups of patients with each patient receiving, at random, only one of the 5 treatments. Strict double-blind conditions prevailed. The randomized allocation was stratified two ways: for moderate or severe initial pain, and also for 3 nurse observers. Within each of these 6 strata separate randomized matched blocks of patients were assigned to the 5 treatment groups. This insured that all groups were evenly balanced with respect to initial levels of pain intensity, and with respect to interobserver variation. It also

insured that all treatment groups were approximately equal in sample size, i.e., 29 to 33 patients each. The 157 cases included 92 with moderate pain and 65 with severe pain. After cross validation of responses, the stratified data were pooled for presentation of results.

Using subjective reports as indices of response, each patient rated pain intensity, pain relief and side effects for 6 hours and reported her ratings to one of the 3 trained nurse observers at uniformly conducted interviews (Bloomfield et al. 1976). All interviews for any one patient were performed by only one observer. Patients were awakened if necessary. At each interview, each patient's estimates of pain intensity (PI) and pain relief (PR) were rated on a four-point verbal ordinal scale. Interviews were done immediately before administration of medication, and 7 times thereafter at intervals of one-half or one hour.

From the original observations, pain intensity difference (PID), summed pain intensity difference (SPID), and summed pain relief (SPR) scores were derived. In addition, a 10 cm visual pain analog scale was used to determine pain analog intensity difference (PAID) and summed pain analog intensity difference (SPAID). The final efficacy variable was global evaluation which was rated on a 0 to 10 verbal ordinal scale. These graded measurements of analgesia were used to measure relative efficacy including peak effects, and time course. Side effects were elicited at the final interview, or earlier, with minimum use of leading questions and without invoking a checklist of possible side effects. Data were recorded on case report forms specifically designed for computer application and were statistically analyzed for treatment group differences by standard parametric and nonparametric statistical tests (Siegel 1956, Morrison 1976).

RESULTS

Three patients were disqualified when it was discovered they had received a prescribed analgesic less than 3 hours before enrollment. Results are therefore based on 154 cases. Initial (0 hour) mean PI values were almost identical (2.37 to 2.45) in all treatment groups (Table I). Subsequently, responses to the 3

Table I. Pain intensity scores (mean ± S.E.) after treatment with ciramadol, codeine and placebo for episiotomy pain

Time (hr)	Ciramadol 60 mg (n = 31)	Ciramadol 30 mg (n = 31)	Ciramadol 15 mg (n = 30)	Codeine 60 mg (n = 33)	Placebo (n = 29)
0	2.42 ± 0.09	2.45 ± 0.09	2.37 ± 0.09	2.39 ± 0.09	2.41 ± 0.09
0.5	1.68 ± 0.14	1.64 ± 0.13	1.70 ± 0.15	1.70 ± 0.14	2.00 ± 0.13
1	1.29 ± 0.14	1.10 ± 0.14	1.17 ± 0.14	1.27 ± 0.13	1.83 ± 0.14
2	1.07 ± 0.13	0.84 ± 0.12	0.97 ± 0.12	1.09 ± 0.15	1.52 ± 0.14
3	1.03 ± 0.16	0.93 ± 0.14	1.00 ± 0.14	1.21 ± 0.17	1.52 ± 0.14
4	0.94 ± 0.17	1.03 ± 0.16	1.00 ± 0.14	1.33 ± 0.17	1.45 ± 0.16
5	1.03 ± 0.16	1.03 ± 0.15	1.17 ± 0.17	1.36 ± 0.17	1.59 ± 0.18
6	1.07 ± 0.15	1.16 ± 0.15	1.10 ± 0.16	1.39 ± 0.17	1.55 ± 0.20

Table II. Relative analgesic efficacy of ciramadol, codeine and placebo after episiotomy based on mean scores of summary variables (number of patients)

Variable	Ciramadol 60 mg	Ciramadol 30 mg	Ciramadol 15 mg	Codeine 60 mg	Placebo
SPID	8.84 (31)§	9.42 (31)∇	8.47 (30)∞	7.58 (33)φ	5.45 (29)
SPR	12.19 (31)§	13.39 (31)∇	12.23 (30)∞	11.12 (33)*	8.59 (29)
SPAID	214.20 (31)*	228.80 (29)§	187.90 (30)§	175.50 (33)φ	114.40 (27)
Global	7.83 (30)§	8.00 (31)ζ/	7.73 (30)§	6.73 (33)	5.76 (29)

§ $p \leq 0.01$, ∇ $p \leq 0.001$, ∞ $p \leq 0.02$, φ $p \leq 0.10$, * $p \leq 0.05$, ζ $p \leq 0.005$ vs placebo; / $p \leq 0.05$ vs codeine (Mann-Whitney test including Bonferroni procedure).

ciramadol doses and codeine tended to be better than responses to placebo.

Table II shows relative efficacy based on six-hour mean scores of all summary variables including derived variables and global evaulation. It shows that all dose levels of ciramadol induced higher mean scores than either codeine or placebo. Ciramadol 30 mg was invariably rated the most effective treatment, followed in order by ciramadol 60 mg, ciramadol 15 mg, codeine 60 mg, and placebo. All 3 dose levels of ciramadol showed significant superiority over placebo, and ciramadol 15 mg and 30 mg, but not 60 mg,exhibited a positive dose-response slope. Codeine 60 mg clearly did better than placebo, but its performance was significant only at the 10 percent level (SPID and SPAID) Moreover global ratings showed that codeine was significantly inferior to the 30 mg dose of ciramadol.

Time-PID effects (Fig 2A) show that all 3 doses of ciramadol appeared to have comparable analgesic time course patterns. Start-

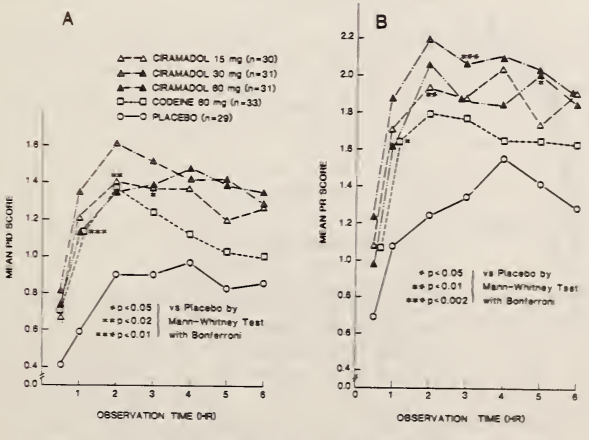

Fig 2 Pain intensity difference and pain relief versus time with single oral doses of ciramadol, codeine and placebo after episiotomy

ing at one hour, separation from placebo seemed equally distinct with each of the 3 doses of ciramadol. Peak effect of the 30 mg dose tended to exceed that of the other 2 dose levels. The separation from placebo seemed to remain intact until the 5th or 6th hour, including a statistical advantage over placebo at several time points with one or more of the dose levels. By contrast, peak effect with codeine was lower than that of all the ciramadol doses, and, while separation of codeine from placebo may have been significant at the first and second hours, thereafter it diminished rapidly indicating a different time-effect pattern from that of the ciramadol doses.

These results are mirrored in the time-PR graph in Figure 2B which shows further that significant responses to ciramadol persisted almost to the end of the 6-hour observation period, despite a suggested natural tendency toward return of pain as reflected in the placebo curve.

Very similar results were also obtained with PAID scores versus time (Fig 3) which, in addition to previously mentioned drug-placebo differences, show that at the second hour the peak effect of ciramadol 30 mg was significantly superior to that of codeine.

Rescue analgesic was requested by a total of 13 patients: 5 in the codeine group, 4 in the ciramadol 60 mg group, 3 in the placebo group, and 1 in the ciramadol 15 mg group. There were no such cases in the ciramadol 30 mg group.

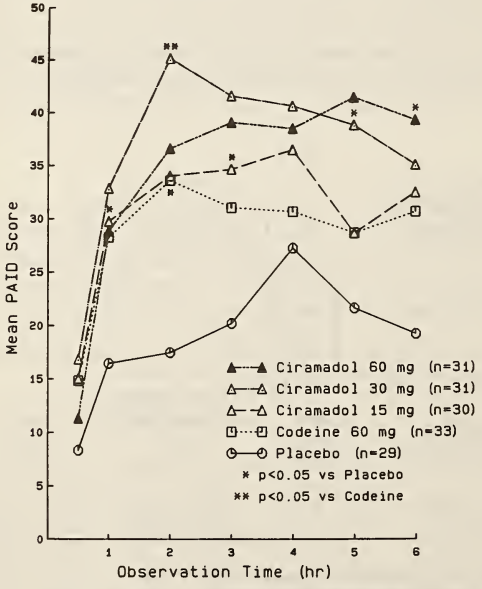

Fig 3 Pain analog intensity difference versus time with single oral doses of ciramadol, codeine and placebo after episiotomy

Table III. Incidence of side effects after treatment with ciramadol, codeine and placebo for episiotomy pain

Side Effect	Ciramadol 60 mg (n = 31)	Ciramadol 30 mg (n = 31)	Ciramadol 15 mg (n = 30)	Codeine 60 mg (n = 33)	Placebo (n = 29)	Total No. Patients (n = 154)
Any side effect†	19*	18**	13	11	7	68[∞]
Drowsiness	12+	13++	6	7	2	40[§]
Dizziness	6	6	7	6	4	29
Nausea	3	2	3	2	0	10
Vomiting	1	2	1	1	0	5
Headache	2	0	1	0	1	4
Weakness	0	1	1	0	0	2
Other	3	1	2	0	1	7

† Some patients reported more than one side effect; * $p \leq 0.02$ vs placebo; ** $p \leq 0.05$ vs placebo; ∞ X^2 (df=4) = 12.41, $p \leq 0.01$; + 2 severe, 4 moderate, 6 mild; $p \leq 0.01$ vs placebo; ++ 9 moderate, 4 mild; $p \leq 0.005$ vs placebo; § H (df=4) = 13.32, $p \leq 0.01$

Taken together, these data demonstrate that ciramadol was an effective analgesic for postepisiotomy pain and, compared to codeine, was more effective and longer acting. However, dose-dependent analgesia was absent with the 60 mg dose of ciramadol, suggesting that a ceiling effect was reached at the 30 mg dose.

Of the 154 patients, 68 spontaneously reported one or more side effects; drowsiness in the majority of cases (Table III). There were 13 cases of drowsiness after ciramadol 30 mg, and 12 after 60 mg, compared to only 6 after 15 mg, 7 after codeine and 2 after placebo. The drowsiness induced by ciramadol seemed dose related, and was statistically significant at the two higher dose levels, but, as was the case with analgesia, a ceiling effect seemed to be reached at the 30 mg dose.

DISCUSSION

These results suggest that in the postepisiotomy pain model single 15, 30 and 60 mg oral doses of ciramadol provide effective analgesia for up to 5 or 6 hours. There is a positive dose-response slope with an apparent ceiling effect reached at 30 mg for both analgesia and side effects. Fifteen mg is near the minimum effective dose, and the optimum dose appears to lie between 15 mg and 30 mg. Peak and summed analgesia with all 3 dose levels of ciramadol tends to exceed that of codeine 60 mg, which appears to have a shorter as well as a weaker effect.

Dose-dependent analgesia was observed with 15 mg and 30 mg of ciramadol, but not with the 60 mg dose. We have interpreted these findings as suggestive of a ceiling effect at the 30 mg dose. Another explanation is possible and relates to the limitations of the bioassay methodology. If responses to the 30 mg dose of ciramadol had reached the limit of the upside sensitivity of the method of measurement, then it would not have been possible to demonstrate increased analgesia with the 60 mg dose even if it were present. Examination of the results for each of the analgesic variables reveals, however, that maximum analgesia (i.e., 90

percent response) was not achieved with the 30 mg dose. Mean peak PID response was 1.6 compared to a theoretical maximum of 2.2. The corresponding values for PR were 2.2 and 2.7, respectively, and for PAID, 45 and 90, respectively. Thus, lack of dose-dependent responses to the 60 mg dose is not likely attributable to the limitation of the upside sensitivity of the methods used to measure analgesia in this clinical trial, and is probably due to a ceiling effect of ciramadol. The side-effect data reported above tend to corroborate this assertion.

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Development of TR5379M (Xorphanol Mesylate), an Oral Analgesic

J. F. Howes and A. R. Bousquet

DEVELOPMENT OF TR5379M AS AN ANALGESIC

For the relief of pain, there still exists the need for an analgesic drug which is active when administered orally and free from the side effects associated with the non-steroidal anti-inflammatory analgesics or the psychotomimetic effects associated with the mixed agonist antagonists. Several compounds of this latter class are available commercially, but all have significant drawbacks to their use. Pentazocine causes psychotomimetic side effects at the upper dose levels (Jasinski et al, 1975) and nalbuphine is poorly available by the oral route (Beaver et al, 1981). Currently available drugs produce some degree of physical dependence liability in rats (Howes, 1981), in monkeys (Cowan, 1973, Villarreal and Seevers, 1971, and Woods et al, 1980), and in humans (Jasinski and Mansky, 1972, Jasinski et al, 1976). Self-administration also has been demonstrated in monkeys with these drugs (Woods, 1977, Hoffmeister et al, 1972). This paper describes the development of a new drug which appears to be free of many of the undesirable effects described above. In addition the compound appears to have an unique pharmacological profile. Herrera et al,(1982) reported that TR5379M is resistant to naloxone antagonism in the guinea pig ileum and blocks the abstinence precipitated by naloxone in morphine-dependent isolated guinea pig ilea.

ANTINOCICEPTIVE AND NARCOTIC ANTAGONIST ACTIVITY IN ANIMALS

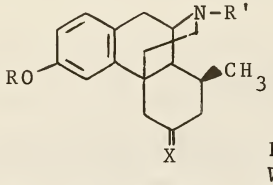
In Table 1, antinociceptive and narcotic antagonist data for TR5379M and some closely related derivatives are presented. Antinociceptive effects were determined using the mouse acetic acid writhing test (Whittle,

1964), and narcotic antagonist activity was evaluated versus morphine using the rat tail flick procedure (Harris and Pierson, 1964). Dr. Jacobson has reported an ED_{50} of 1.3 in the Nilsen Test.

Two compounds, I and TR5379, were selected for further development.

Table 1

ANTINOCICEPTIVE ACTIVITY AND NARCOTIC ANTAGONIST ACTIVITY OF TR5379 AND RELATED COMPOUNDS



	R=	X=	R'=	ED_{50}-Mouse Writhing mg/kg,s.c.	AD_{50} Rat Tail Flick mg/kg,i.p.
	CH_3	O	CH_2-cyclopropyl	0.24 (0.13-0.45)	1.45(0.49-4.3)
	H	O	CH_2-cyclopropyl	3.7 (1.1-12.2)	0.65(0.24-1.8)
	CH_3	CH_2	CH_2-cyclopropyl	3.2 (1.8-5.6)	3.8(1.8-8.1)
	H	CH_2	CH_2-cyclopropyl	1.7 (0.7-4.0)	0.3(0.15-0.6)
	CH_3	O	CH_2-cyclobutyl	0.54 (0.36-0.8)	6.4(2.2-18.2)
(I)	H	O	CH_2-cyclobutyl	0.11 (0.01-1.1)	1.05(0.37-3.0)
	CH_3	CH_2	CH_2-cyclobutyl	6.4 (2.2-18.5)	5.5(2.9-10.4)
(TR5379)	H	CH_2	CH_2-cyclobutyl	0.18(0.05-0.62)	0.83(0.33-2.1)
	Butorphanol			0.15(0.06-0.4)	0.89(0.43-4.2)
	Pentazocine			3.7(2.45-5.5)	10.4(39-28.7)
	Nalbuphine			1.6(0.25-10.5)	6.6(1.6-27.9)
	Morphine			0.79(0.42-1.5)	---

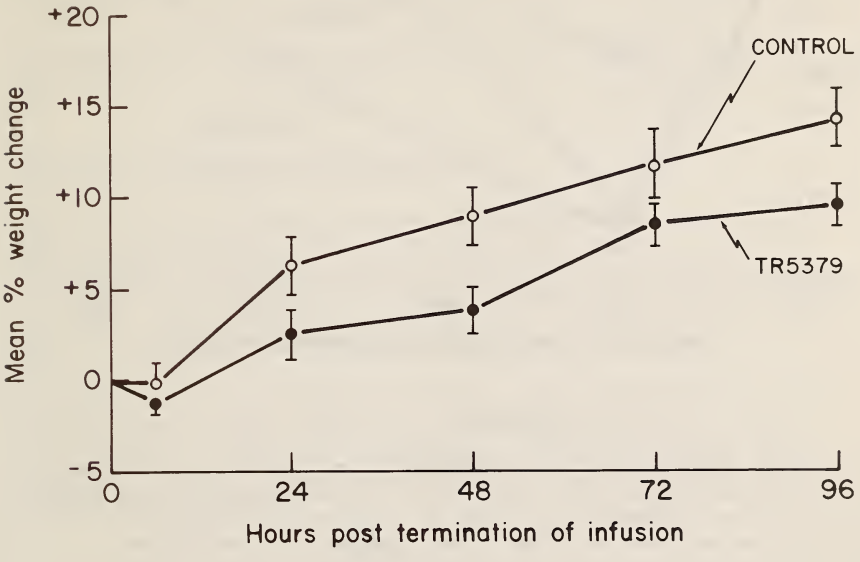
PHYSICAL DEPENDENCE LIABILITY OF TR5379 AND (I)

Both compounds were studied using the rat infusion procedure (Howes, 1981). Compound (I) showed a weak primary dependence in this procedure, whereas TR5379 was free of primary dependence (Figure 1).

In the morphine-dependent rat TR5379M did not substitute for morphine, whereas compound I substituted partially (Figure 2). In morphine-dependent rats TR5379 caused a precipitation of withdrawal (Table 2).

Figure 1

Mean percent weight change of rats following the abrupt termination of a six-day infusion of either saline (○) or 40mg/kg/day TR5379 (●). Points represent the means of six animals and the vertical bars are standard errors. *Statistically significant from control values.



In the monkey (Aceto et al, 1981) TR5379M did not substitute for morphine, and was active as an antagonist causing the precipitation of withdrawal at doses down to 0.125mg/kg s.c. (Table 3).

Figure 2

Mean percent weight change of rats following the termination of a six-day morphine infusion. For the first 24 hours, the rats were infused with a solution of the test substance, which was terminated at 24 hours. The test substances were compound I (■), TR5379 (●) and saline (○). Points represent the means of six animals, and the vertical bars are standard errors.

*Statistically significant from control values ($P<0.05$)

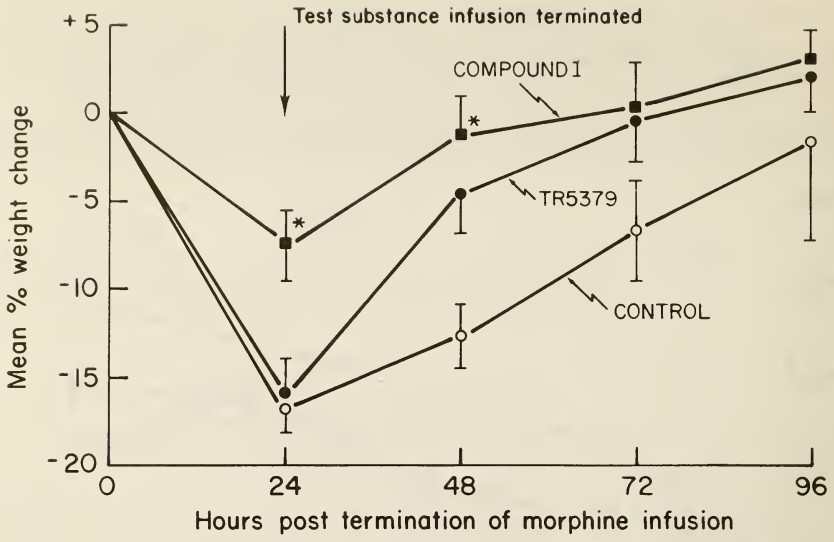


Table 2

The acute administration of TR5379, naloxone or saline to rats made physically dependent on morphine. The data are means and standard errors or ratios of animals showing the effect to the total number in the group. The quantitation of each symptom is described in the methods. * Denotes significant differences ($P<0.05$) vs controls; † Denotes significant differences ($P<0.05$) vs naloxone.

Symptom	TR5379 (3.0mg/kg s.c.)	Naloxone (2.0mg/kg i.p.)	Saline
Teeth chattering	3.25±0.85*	3.20±1.01*	0.00
Tremors	4.25±1.25*	7.20±1.61*	0.00
Chewing	4.00±1.23*	3.40±1.12*	0.00
Wet Dog Shakes	23.25±4.06*†	8.20±2.67*	0.00
Irritability	0/4†	5/5*	1/5
Aggression	0/4	1/5	0/5
Vocalization	0/4	1/5	1/5
Diarrhea	3/4*	3/5*	1/5
4hr weight loss (%)	10.59±1.69*	6.22±1.01*	2.14±0.71

Table 3

PHYSICAL DEPENDENCE LIABILITY DATA FOR TR5379 IN MONKEY

Procedure	Doses Used (mg/kg s.c.)	Result
Single Dose Suppression	1.0, 2.0 & 4.0	No Substitution
Precipitated Withdrawal	0.125, 0.25, 0.5, 2.0, 4.0 & 8.0	Withdrawal signs observed at all doses

STUDIES IN HUMAN VOLUNTEERS

TR5379M was studied in human volunteers at the Ohio State University under the direction of Dr. J. R. Bianchine. TR5379M is well tolerated in normal human volunteers at doses up to and including 10 mg given orally. Marked pupil constriction was observed in subjects receiving 5.0 and 10.0 mg.

Several ongoing phase II studies with TR5379M are demonstrating a high degree of analgesic efficacy with this agent. Compared to codeine, TR5379M has a slower onset of action but a long duration of action. Side effects are minimal.

Table 4

Side Effects	P	0.5mg	1.0mg	2.0mg	5 0mg	10.0mg
Cold						1/3
Sweating					1/9	1/3
Dry Mouth					1/9	1/3
Nausea						1/3
Drowsiness	1/10	2/3			6/9	2/3
Dizziness		1/3			5/9	1/3
Depression						1/3
Lethargy						1/3
Anorexia						1/3
Weakness						1/3
Pallor						1/3
Confusion		1/3			1/9	1/3
Headache	3/10				1/9	1/3
Euphoria						1/3

Table 4 (continued)

Side Effects	P	0.5mg	1.0mg	2.0mg	5.0mg	10.0mg
Light-headed	1/10				1/9	
Tinnitus		1/3				
'High'				1/3		
Abdominal Pain					2/9	
Insomnia					4/9	
Blurred Vision					1/9	
Anxiety					2/9	
Disoriented					1/9	
Warm					1/9	
Frequent Urination					1/9	
No Effects	6/10	0/3	3/3	2/3	1/9	1/3

CONCLUSIONS

Data generated in experimental animals indicate that TR5379 is active as an antinociceptive with a low incidence of side effects. Preliminary studies in human volunteers confirm the low incidence of side effects at doses which are well absorbed orally.

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Intravenous Hydromorphone: Effects in Opiate-Free and Methadone Maintenance Subjects

Mary E. McCaul, Maxine L. Stitzer, George E. Bigelow, and Ira A. Liebson

Methadone maintenance serves two functions: it prevents the onset of withdrawal signs and symptoms in opiate-dependent patients, and it attenuates the euphoric effects of opiate administration by establishing tolerance to opiate drugs. Two earlier studies examined the euphoric response to opiate administration during induction onto methadone. Dole, Nyswander and Kreek (1966) demonstrated a progressive blockade of heroin's euphoric effects as a result of increasing time in treatment and increasing dose of methadone during methadone induction. Jones and Prada (1975) reported that self-administration of intravenous hydromorphone decreased during induction onto 100 mg/day methadone; pupillary constriction and liking scores following intravenous hydromorphone also gradually decreased to placebo levels during this induction procedure.

Although these earlier reports suggest that there is little or no effect of supplemental opiate administration following induction onto high doses of methadone, methadone maintenance clinics frequently report continued illicit opiate use by the maintenance clients. In an effort to increase understanding of this continued supplemental opiate use in methadone maintenance clients, the present study examined the physiological and subjective effects of intravenous hydromorphone in long-term methadone maintenance patients. Drug effects were also assessed in a group of post-addict subjects who were not currently dependent on or tolerant to opiates; results from this group provided a standard against which to compare the drug effects in methadone maintenance subjects.

Methods

Subjects. The subjects were 10 males, ranging in age from 25 to 35 years of age. All subjects had extensive histories of intravenous opiate use; five subjects were currently opiate-free and five were maintained on 50 - 60 mg/day methadone. The methadone maintenance subjects had been receiving a stable dose of methadone for at least nine months at the time of the study. Partici-

pants were fully informed of the experimental protocol and risks at the start of the study and were reimbursed for their participation.

Procedure. Sessions were conducted two or three days per week with at least one nonstudy day separating sessions. For methadone maintenance subjects, sessions were conducted approximately 24 hours following their last dose of methadone.

A venous catheter was placed in the subject's arm prior to the start of each session. The vein was kept patent by a saline drip, which was removed approximately a half-hour following the injection. Subjects were seated in a quiet room with the experimenter throughout the three hour session.

A minimum of 30 minutes elapsed between the start of the session and drug administration. Physiological measures stabilized during the first 15 minutes. Baseline data for each session were collected during the next ten minute period. Five more minutes then elapsed before drug administration. At the end of this half-hour period, the saline drip was clamped off and the injection was given via the catheter. Data collection continued for two hours following the injection.

All subjects were exposed to several different doses of hydromorphone and to placebo control injections. Four of the five opiate-free subjects received 0, 2, 4 and 6 mg doses of hydromorphone; the other opiate-free subject only received doses of 0, 2 and 4 mg. All five methadone maintenance subjects received 0, 10, 14 and 18 mg doses of hydromorphone. Subjects received each dose at least twice in a random sequence; doses were administered under a double-blind procedure.

The following measures were continuously recorded throughout each session: 1) heart rate, using EKG leads on the chest; 2) skin temperature, using a probe on the finger tip; 3) respiration, using a mercury strain gauge stretched across the abdomen; and 4) blood pressure, using a cuff that automatically inflated and recorded pressure once every minute (Roche Arteriosonde #1216). In addition, a number of measures were intermittently recorded during each session. A pupil photograph was taken approximately 15 minutes prior to the injection and six times following the injection, using a Polaroid camera with 3X magnification. Four subjective report forms were also administered approximately 15 minutes prior to the injection and four times following the injection at half-hour intervals. Subjective report forms included: 1) an analogue high scale on which subjects were asked to rate their current degree of "high" from 0 to 100; 2) the short form of the Addiction Research Center's MBG (Morphine-Benzedrine Group) scale (Haertzen 1974); and 3) a 32-item adjective checklist, which included the Fraser Single-Dose Opiate Questionnaire (Fraser et al. 1961), as well as additional signs and symptoms characteristic of opiate effects. Each time the self-report forms were administered during the session, subjects were instructed to

respond according to the way they felt at the present moment.

Data analysis. Physiological data are presented using "difference from control" scores. These were calculated by subtracting the mean of the 10-minute baseline measures from the mean of the 2-hour postinjection measures for each session. These difference scores were averaged across replications at each dose for each subject and were then summarized across subjects at each dose. Responses to MBG and adjective checklist self-report scales were also adjusted with respect to predrug data by calculating difference scores. Scores for the Fraser Single-Dose Opiate Questionnaire were derived using the weighted scoring system introduced by Martin and Fraser (1961). Dose-effect data for each measure are presented graphically using the mean of the 2-hour postinjection period. Data are presented separately for the postaddict subjects and the methadone maintenance subjects.

Results

None of the baseline physiological measures were significantly different in the opiate-free subjects and in the methadone maintenance subjects 24 hours following their last dose of methadone; for example, mean pupil diameter prior to the injection was 6.3 mm in opiate-free subjects and 6.1 mm in methadone maintenance subjects. For both methadone maintenance and opiate-free subjects, intravenous hydromorphone produced changes in physiological and subjective measures when compared with placebo administration. However, the magnitude of the drug effect was generally smaller in the methadone subjects than in the opiate-free subjects even though the maximum drug dose employed was three times higher for the methadone subjects.

Figure 1 summarizes the effects of intravenous hydromorphone on pupil diameter in both opiate-free and methadone subjects. There was little change in pupil diameter for either group following the placebo injection. In opiate-free subjects, hydromorphone produced a graded increase in pupillary constriction from 2.2 mm following the 2 mg dose to 3.7 mm following the 6 mg dose. In methadone maintenance subjects, there was little difference in the amount of pupillary constriction following the range of test doses; pupillary constriction averaged 1.9 to 2.3 mm, approximately the same constriction seen in opiate-free subjects following administration of the lowest dose of drug.

Figure 2 summarizes the dose-dependent effects of hydromorphone on respiration for the two groups of subjects. There was little change from baseline respiration rates following placebo administration in either group. In contrast to the effects of hydromorphone on pupil diameter, hydromorphone produced similar decreases in respiration rates for both opiate-free and methadone maintenance subjects; for both groups, respiration decreased an average of 2 to 3 breaths per minute during the 2-hour postinjection period. While the magnitude of the effect was similar following the highest dose in both groups, this effect was achieved at

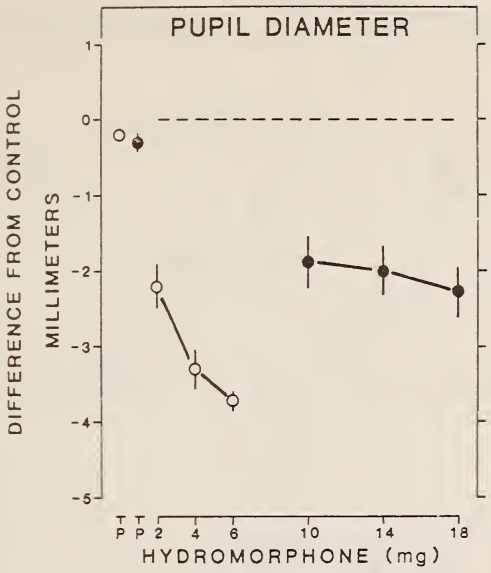

FIG. 1. *The effects of intravenous hydromorphone on pupil diameter in opiate-free subjects (○) and methadone maintenance subjects (●). Unconnected symbols represent the results of placebo administration. Error bars indicate ± SEM.*

a dose three times greater in methadone maintenance subjects than in opiate-free subjects (6 mg vs 18 mg).

In contrast to the similarity of the baseline physiological measurements observed in the two groups of subjects, baseline subjective scores for the two groups were significantly different on three of the four self-report scales. Baseline scores for the methadone maintenance subjects were significantly lower than for opiate-free subjects on the adjective checklist, the Fraser Single-Dose Opiate Questionnaire and the MBG scale. Although methadone maintenance subjects did not appear to be experiencing physical symptoms associated with withdrawal during the baseline period, these differences could be related to the 24-hour lapse since ingestion of their last dose of methadone.

As shown in Figure 3, there was little or no change from baseline on subjective report measures following placebo administration in either group. For opiate-free subjects, there were marked, dose-related increases on all subjective measures following 2 and 4 mg of hydromorphone, with little or no further increase in scores following 6 mg. In contrast, for methadone maintenance subjects,

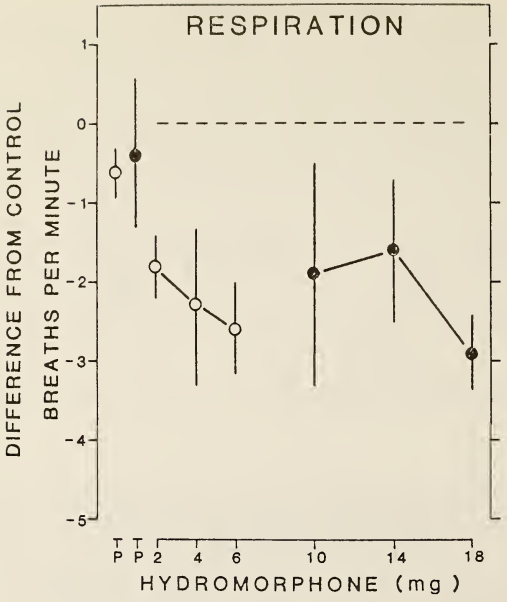

FIG. 2. *The effects of intravenous hydromorphone on respiration in opiate-free subjects (o) and methadone maintenance subjects (•). Unconnected symbols represent the results of placebo administration. Error bars indicate ± SEM.*

scores on the Adjective Checklist and Analogue High scale increased only slightly over the range of hydromorphone doses employed. Scores on the Fraser Single-Dose Opiate Questionnaire and the MBG scale were increased in a dose-related manner following administration of hydromorphone to methadone maintenance subjects; however, the absolute magnitude of the increase on the Single-Dose Questionnaire was less for methadone maintenance subjects than for opiate-free subjects. The MBG scale was the only self-report scale on which opiate-free and methadone maintenance subjects showed comparable increases in score.

Discussion

For both methadone maintenance and opiate-free subjects, intravenous hydromorphone produced changes in physiological and subjective measures as compared with placebo administration. However, the absolute magnitude of the drug effect was generally smaller in the methadone maintained than in the opiate-free subjects even though the maximum hydromorphone dose employed was three times higher for the methadone subjects. Furthermore, in contrast to the opiate-free subjects, there was little graded

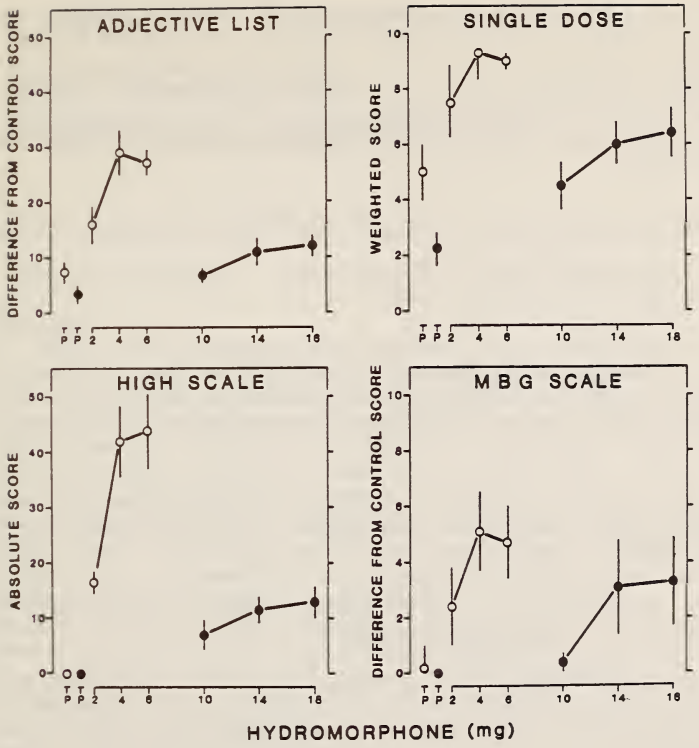

FIG. 3. *The effects of intravenous hydromorphone on four subjective report measures in opiate-free subjects (○) and methadone maintenance subjects (●). Unconnected symbols represent the results of placebo administration. Error bars indicate ± SEM.*

effect of the range of test doses in methadone maintenance subjects. Both the blunted magnitude of the drug effect and the lack of clear dose-effect relationships suggest that there is tolerance to the effects of intravenous hydromorphone on physiological and subjective measures in methadone maintenance subjects as compared with opiate-free subjects.

The results of this study differ from the results of previous research on supplemental opiate effects during methadone induction. Those studies reported little or no difference between opiate and saline administration following induction onto high doses of methadone (Dole, Nyswander and Kreek 1966; Jones and Prada 1975); however, in the present study, there were clear differences between placebo and hydromorphone administration on all measures in patients maintained on moderate doses of methadone. These findings suggest that the effects of opiate adminis-

tration are diminished but not eliminated in methadone maintenance clients, and that these patients continue to experience the typical range of physiological and subjective responses to intravenous opiate use during long-term methadone maintenance. These results may explain in part the observation that some methadone maintenance patients continue to use supplemental opiate drugs during treatment.

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The Effect of Morphine on Symptoms of Endogenous Depression

Michael Feinberg, Jean-Paul Pegeron, and Meir Steiner

INTRODUCTION

Opium has been used to relieve the troubled mind for countless years, and has been recommended for the treatment of a wide range of mental illnesses for centuries. With the isolation of morphine and the invention of the hypodermic syringe, subcutaneous administration of morphine came to replace oral opium in the treatment of seriously ill patients, although the use of opium continued. Morphine was considered a sedative par excellence, effective when a wide variety of drugs had failed. Indeed, some physicians who recommended it said that its effect was secondary to the sleep it produced, especially in depressed patients (McDiarmid, 1876; Russell, 1860). In the past 40 years, morphine has been replaced by other somatic treatments which are thought to be more specific and which do not have the addiction liability associated with the narcotics. More recently, following the discovery of the endorphins, a number of investigators have suggested that they may be involved in the pathophysiology of mental illness. Some have postulated a functional excess of endorphins in, for example, schizophrenia (Bloom et al., 1976), and have treated patients with narcotic antagonists (Berger et al., 1981). Others have suggested that there may be a functional deficit of endorphins, and have administered beta-endorphin with good results (Kline et al., 1977; Gerner et al., 1980). This resurgence of interest in the association between narcotics and mental illness suggests that a careful reading of the older clinical literature may point the way toward fruitful experiments which will shed light on the pathophysiology of some mental illnesses and may suggest radically new treatments. Comfort (1977) has briefly reviewed the literature written in English.

Recent clinical and laboratory data suggest that some patients with melancholia (endogenous depression; ED) may have higher than normal levels of beta-endorphin. Carroll et al. (1981) have shown that 2/3 of patients with ED fail to suppress cortisol secretion for 24 hours after oral dexamethasone. These patients also have high cortisol levels throughout the day and lose the normal diurnal rhythm of cortisol production. Other evidence suggests that these high cortisol levels are secondary to high ACTH levels (Reus et al., 1982) and also that the increase in secretion of ACTH is accompanied by an increased secretion of beta-endorphin (Guillemin et al., 1977). Thus it may be most

fruitful to begin with the literature on the treatment of affective disorders, particularly melancholia, with opiates.

We have reviewed the clinical literature on the treatment of melancholia with morphine or opium, covering the years from 1850 to 1960, to address several questions:

1. Is morphine effective in relieving the symptoms of endogenous depression?
2. If so, is this merely nonspecific sedation, or is there some more specific treatment of symptoms?
3. Does the relief of symptoms persist after the administration of morphine is stopped?
4. How do depressed patients respond to morphine? What dose is needed for relief of symptoms, or for sedation? What is the incidence of tolerance and dependence?

REVIEW OF THE LITERATURE

Our review concentrated on articles written in English and German, and included a few written in French. The literature was translated by the authors, who are psychiatrists practicing in English. One author (M.S.) is a native speaker of German; another (J-P.P.), of French. We will address the questions above in the order given, and have included synopses and evaluations of the literature reviewed in an Appendix. In order to compare studies, it is necessary to assume that all the opium used contained 10 percent morphine base as the sole active ingredient, even though this may not be true. It is difficult to compare reports about oral morphine or opium with those discussing the effects of subcutaneous administration of morphine salts because of the uncertainties of absorption after oral administration and of first-pass hepatic metabolism. McDiarmid (1876) cites these uncertainties as one reason for preferring parenteral administration. The recommended daily dose of morphine ranges from about 7 mg hs to 90 mg per day. In the discussion that follows, morphine is assumed to include both morphium and opium unless otherwise noted. Opium was given by mouth in all the references cited; morphine itself was given by mouth in one study, by Mickle (1874).

The interpretation of the literature cited is made more difficult by the usual clinical course of endogenous depression (melancholia). It is most commonly an episodic illness, with each episode lasting some 4 to 12 months if untreated. The patient usually remains well until the next episode, which not uncommonly begins 12 months after the previous one began.

Nearly every author cited concluded that morphine provided symptomatic relief in melancholia, and some suggested that morphine cured the patient. Kielholz (1959) compared opium with imipramine and concluded that opium produced symptomatic relief but that the symptoms might return if treatment were stopped. (It is interesting to note that this represents the current clinical

wisdom about imipramine: the symptoms may return if administration of the drug is stopped too early.) Tigges (1864) was the only author who found opium useless in the treatment of melancholia. He described the treatment of 39 patients, and provided a good deal of information about each patient's history, symptoms, and treatment. He concluded that the poor response may have been caused by the patients' having chronic, rather than acute, melancholia. It is equally likely that the lack of response was due in part to the relatively low doses of opium used. Some older textbooks of psychiatry recommend opium as a sedative-hypnotic in endogenous depression (Bucknill & Tuke, 1858; Cramer et al., 1907; Maudsley, 1867), while others found it useless (Henderson and Gillespie, 1933). The latter did not comment on the doses used, and the former only occasionally provided guidelines for its use.

Every author found that morphine was an effective sedative if the dose were high enough. Even Tigges (1864) found that morphine (but not opium) was initially effective as a sedative, although this effect was soon succeeded by excitation, suggesting the development of tolerance. McDiarmid (1876) and Russell (1860) believed that the relief of other symptoms was secondary to the sleep produced by morphine. Kielholz (1959) and Marce (1857) found, however, that patients improved clinically despite the persistence of the sleep disturbance which is such a common feature of melancholia.

Nearly all of the patients described were psychotic. Morphine had an antipsychotic effect out of proportion to its effect on other symptoms, such as depressed mood. Kielholz (1959), Mickle (1874), and Marce (1857) were quite specific about this, and Ziehen (1889) found that the presence of hallucinations predicted a good response to opium. These reports are even more interesting in light of the more recent finding that psychotically depressed patients may not respond to treatment with tricyclic antidepressants (Glassman et al., 1975).

Some of the papers cited describe psychotic patients who probably did not have endogenous depression (Engelken, 1851; Knecht, 1872; Voisin, 1881; 1891); in these cases the antipsychotic effect was clearly separate from an antidepressant (or antimelancholic) effect. The antipsychotic effect of morphine, found in a wide variety of patients, is difficult to reconcile with the current theory that psychosis may be due to a functional excess of endorphins and be relieved by narcotic antagonists (Bloom et al., 1976; Berger et al., 1981). Gold et al. (1977) have suggested that morphine may have an antipsychotic effect, based on the morphine-induced increase in plasma prolactin.

Only a few of the authors mentioned tolerance or physical dependence. Mickle (1874) did not find that tolerance developed, and believed that this was because of the low dose of morphine, 15-20 mg, tid. This is not, by most standards, a low dose, and it is likely that tolerance does ordinarily develop to this dose.

The French authors, Marce (1857) and Voisin (1881; 1891) clearly described tolerance and physical dependence in their patients, the latter at doses of morphine similar to those used by Mickle. Voisin also described an increased sensitivity to morphine, which occurred suddenly when patients became well. He could find no reason for this, or for the wide range of sensitivity to morphine in his patients; he said that he'd asked Claude Bernard, who was similarly puzzled.

CONCLUSIONS

The available evidence clearly suggests that morphine produces symptomatic relief in melancholic patients, and that this relief is out of proportion to any sedative effects. These effects seem to be dose related, as authors using lower doses (<60 mg of morphine/day) reported fewer responses to treatment than did those using higher doses. It is likely that rather than being a cure, this is symptomatic relief similar to that provided by antidepressant drugs, although most of the authors do not give enough information to allow a clear decision. This finding suggests that abnormal functioning of an endorphin "system" may be responsible for some of the symptoms of melancholia. It is tempting, and may be fruitful, to speculate that this abnormal functioning may underlie the illness itself. It is also possible that morphine, an artificial endorphin, acts to remedy symptoms caused by abnormal function elsewhere in the brain.

The evidence suggests that we should mount a double-blind placebo-controlled study of morphine or other centrally acting endorphin agonist in patients with melancholia. Such a study should probably include a narcotic antagonist and one or more of the partial agonists. The drugs used should be selected for their differential effects on the several postulated endorphin receptors in the brain.

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The Effects of Two Non-Pharmacological Variables on Drug Preference in Humans

H. deWit, C. E. Johanson, E. H. Uhlenhuth, and S. McCracken

The question of whether benzodiazepines, and in particular diazepam, should be considered drugs of abuse has recently become a matter of considerable controversy. On the one hand, there is concern over the large number of prescriptions that are written for these drugs every year. On the other hand, there is very little evidence that the benzodiazepines are being used inappropriately, i.e., nontherapeutically, by the vast majority of people exposed to them. Because of the limitations of clinical surveys and case reports as a reliable source of data, this issue has also become the subject of experimental research in both animals and humans (Griffiths and Ator, 1980). Experimental techniques have been developed in the laboratory to measure the dependence potential of drugs by assessing their efficacy as positive reinforcers of behavior. In these experiments, as well, there is little evidence that diazepam is similar to other, clearly abused drugs. For example, there are only isolated reports of animals self-administering benzodiazepines, and results from our laboratory indicate that in normal human volunteers, diazepam also does not act as an effective reinforcer (Johanson and Uhlenhuth, 1980a). The present experiments further explored the reinforcing properties of this drug in human volunteer subjects.

These studies utilized a choice procedure in which a drug was compared to placebo. The experiments consisted of two phases, a sampling phase followed by a choice phase, in which subjects were allowed to ingest the substance they preferred. The number of times that a drug was chosen (compared to placebo) was considered an indication of its positive reinforcing efficacy in this situation. In addition to this behavioral measure of preference, the subjects also were asked to complete subjective effects questionnaires before and at various times after ingestion of the drug, providing a quantitative and temporal profile of the drug's effects on mood. It is important to be able to examine the degree of concordance between the behavioral measure of positive reinforcement (choice) and the subjective mood effects, particularly since the subjective effects of drugs traditionally have been used as indicators of dependence potential.

In the previous study using this procedure (Johanson and Uhlenhuth 1980a), normal, healthy volunteer subjects preferred placebo over 5 and 10 mg diazepam. A dose of 2 mg diazepam was chosen equally as often as placebo. At the two higher doses there were clear, dose-dependent changes in subjective effects on several subscales of an experimental version of the Profile of Mood States (POMS; McNair et al, 1971) after drug ingestion, showing effects that were consistent with the drug's known sedative properties (e.g., decreased Vigor and Arousal, increased Fatigue). It is clear that the experimental paradigm is sensitive to the reinforcing properties of drugs since in a comparison between amphetamine, a highly abused drug, and placebo, these same subjects showed a clear preference for amphetamine (Johanson and Uhlenhuth, 1980a).

Despite the experimental evidence suggesting that diazepam is not an effective positive reinforcer, there is one report that is not consistent with this notion. Griffiths et al. (1980) have shown that inpatient subjects do show a strong preference for diazepam over placebo. However this study differed from studies in our laboratory in terms of the subject population used, the doses of drug used, and the procedural details of the experiments. While these differences make it difficult to identify the variables that might account for the discrepancy between their results and ours, it is clear that further research is needed to explore the variables that influence the reinforcing properties of this drug.

The present experiments explored this problem by manipulating two nonpharmacological variables that might increase the ability of diazepam to serve as a positive reinforcer. One of these was to determine whether preference for the drug would be different for people who are anxious. The possibility existed that the therapeutic value of the drug, its anxiolytic property, would make it a positive reinforcer. Secondly, the absence of a preference for diazepam in the earlier study may have been due to the drug's mild sedative effects. Since most of the subjects were university students and employees whose work required a high level of activity and alertness, the sedative effects of the drug might have been too disruptive. To test this hypothesis, a group of normal nonanxious subjects ingested the drug late in the day, when the demands on concentration and activity were presumably less. In addition to these two groups of subjects, a group of normal subjects who ingested the drug in the mornings was used for purposes of comparison to the previous study.

METHOD

Subjects. Three groups of subjects, aged 21 to 35, were tested in each of three experiments. On the basis of a complete psychiatric interview, 24 subjects were selected who were considered normal, and 12 subjects (Anxious Group) were selected on the basis of having a DSM III (A.P.A., 1980) Generalized Anxiety Disorder. Twelve normal subjects served as the Control Group and the remainder were assigned to the Afternoon Group, who reported to the laboratory in the late afternoon rather than the morning. Subjects with a history of primary depression or drug abuse were excluded from the study. All subjects signed an

informed consent before participation that detailed the experimental protocol and informed the subjects of any possible drug effects they might experience.

Procedure. All subjects participated in three separate choice experiments, each comparing a drug to placebo. Drug and placebo were prepared in opaque gelatin capsules with dextrose powder used as filler. The procedure for each experiment was identical except for the drug used, which was either 5 or 10 mg diazepam, or 5 mg d,l-amphetamine. The order of presentation of these experiments was randomized across subjects.

Each experiment consisted of 9 sessions, of which the first four were sampling days, and the following 5 were choice days. Subjects in the Control and Anxious Groups reported to the laboratory between 9 and 10 am, and the subjects in Afternoon Group came between 4 and 5 pm to ingest their capsule. When a subject arrived, she/he filled out mood questionnaires (see below) and then received a distinctively colored capsule containing either drug or placebo for immediate ingestion. Approximately half the subjects received drug during sessions 1 and 3 and placebo on sessions 2 and 4, and the order was reversed for the other half. For each subject, each drug was dispensed in a capsule of a consistent and distinctive color in order to facilitate identification during choice sessions. Capsule colors were assigned randomly across subjects to minimize the influence of color preference. Subjects were instructed during the initial four sessions (sampling) to note the capsule colors, to try to associate each of the two colors with the effects of the substances contained in them and to remember that the same drug was always contained in a capsule of the same color. After ingesting the capsule, subjects were free to leave the laboratory. They took three additional sets of mood forms with them, to be completed 1, 3 and 6 hours later. During the last five sessions, the procedure was identical in every respect except that the subjects were given a choice of the two colored capsules to ingest.

The mood questionnaires to be completed were the Addiction Research Center Inventory (ARCI) (Haertzen, 1974) and an experimental version of the Profile of Mood States (POMS). The ARCI consists of 49 true/false questions separated into 5 clusters described as measuring stimulant-like effects (two subscales), euphoria, sedation and dysphoria. The POMS consists of 72 adjectives commonly used to describe momentary mood states. Subjects indicate how they feel at the moment in relation to each of the adjectives on a 5-point scale, ranging from 'not at all' to 'extremely.' There are 8 clusters of items (Anxiety, Depression, Anger, Vigor, Fatigue, Confusion, Friendliness and Elation) and two additional derived subscales (Arousal and Positive Mood). The results of the subjective effects rating scales reported here are based only on data from the first four sessions (sampling sessions) of each experiment.

RESULTS AND DISCUSSION

The number of subjects in the Control Group who chose each drug on 0-5 occasions is illustrated in figure 1. T-Tests for correlated measures

were used to determine whether the mean number of drug choices differed statistically from chance (2.5). Amphetamine at 5 mg was

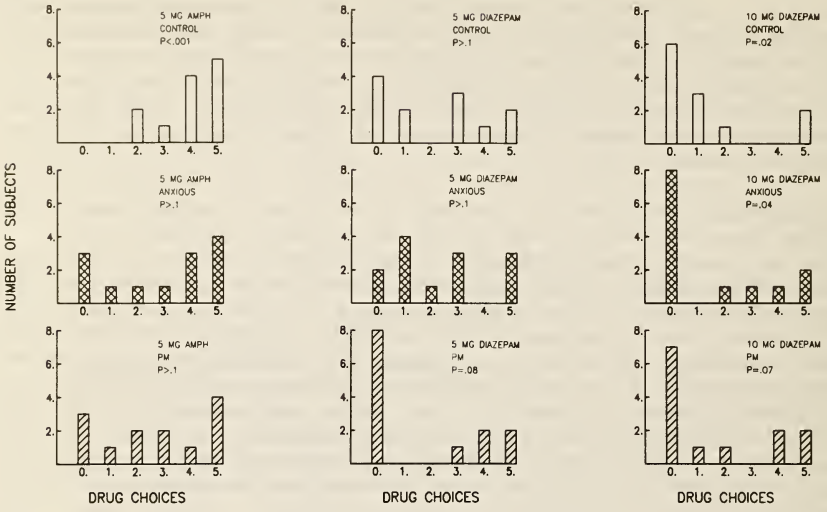

Figure 1: Number of subjects choosing drug 0-5 times.

chosen over placebo on 80 percent of the occasions ($p < .01$); this preference for racemic amphetamine is similar to that found for d-amphetamine in previous studies (Johanson and Uhlenhuth, 1980a,b), despite the fact that the racemic amphetamine may be less potent than the d-isomer. Consistent with earlier findings, the Control subjects did not show a preference for diazepam at either dose. The 5 mg dose was chosen about equally as often as placebo (41 percent drug choice) while at the higher dose of diazepam (10 mg), subjects preferred placebo to the drug (25 percent drug choices; p=.02). Subjects who chose diazepam 4 or 5 times at the 5 mg dose were not usually the same subjects who chose drug 4 or 5 times at the 10 mg dose.

The subjects in the Anxious Group did not choose diazepam over placebo at either of the doses tested. They chose 5 mg diazepam about as often as placebo (48 percent), and preferred placebo to the 10 mg dose of diazepam (29 percent drug choices). Unexpectedly, the Anxious subjects chose amphetamine less often than the Control Group (58 percent - drug choice). These results are apparently inconsistent with an earlier finding (Uhlenhuth, Johanson, Kilgore and Kobasa, 1981) that normal subjects who chose amphetamine 5 out of 5 times had higher pre-drug scores on the Anxiety subscale of the POMS than subjects who did not choose the drug consistently.

For the group of subjects who ingested the drug late in the day, the drug preferences in the three experiments were similar to those seen in the Anxious Group. That is, amphetamine was chosen equally as

often as placebo (53 percent), while placebo was preferred to both 5 and 10 mg dose of diazepam (32 percent drug choice in each case).

Amphetamine produced surprisingly little effect on the subjective effects questionnaires for the Control Group despite these subjects' clear preference for the drug. None of the subscales of the POMS showed a significant drug x hour interaction. It is notable, however, that the one scale that did show a significant effect for this group was the MBG Scale of the ARCI, a scale that has been associated with "euphoric" drug effects. These modest changes in subjective effects after amphetamine are in contrast to previous studies with the d-isomer, which have shown clear changes in subjective effects. This difference may indicate that the dose of drug used approached the threshold of discrimination. Nevertheless, this discrepancy across measures suggests that preference is a more sensitive indicator of a drug's reinforcing properties than scores on these subjective effects questionnaires.

For the Anxious Group, amphetamine increased scores on Vigor and Arousal subscales of the POMS at hours 1 and 3, while for the Afternoon Group, no significant drug effects were observed.

Diazepam produced clear dose-dependent effects on both the POMS and the ARCI (figures 2 and 3). Increased scores on POMS subscales

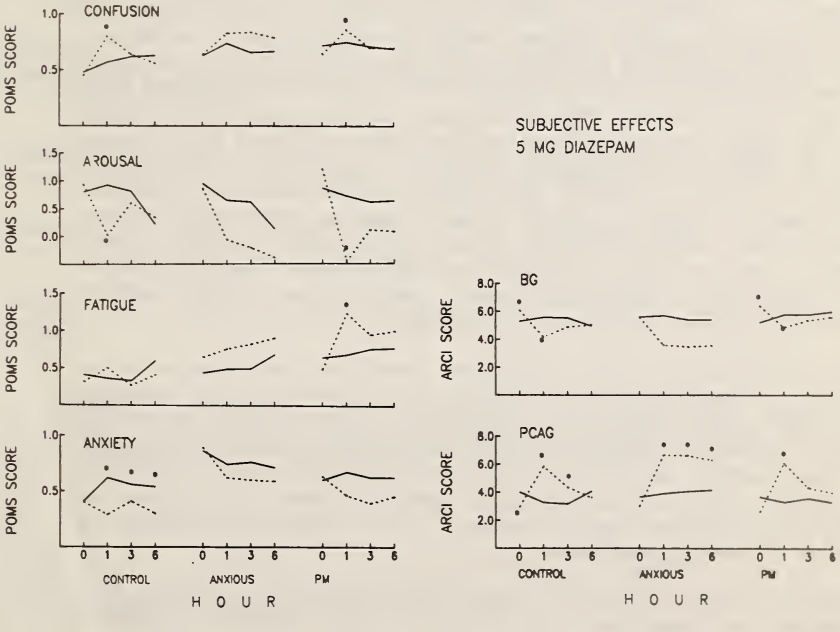

Figure 2: POMS and ARCI scores for placebo (solid lines) and 5 mg diazepam (broken lines). Asterisks show significant ($p < .05$) differences.

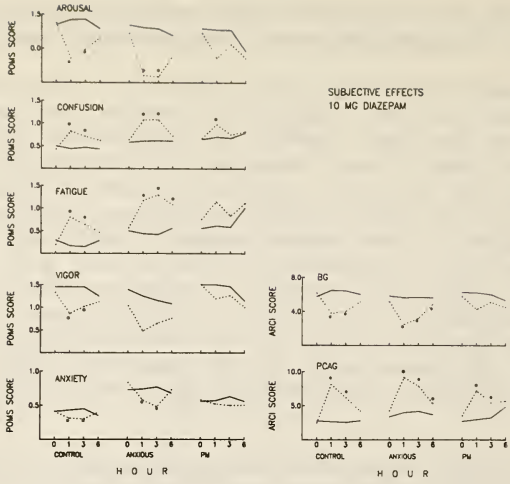

Figure 3. POMS and ARCI scores for placebo (solid lines) and 10 mg diazepam (broken lines). Asterisks show significant ($p < .05$) differences.

Confusion and Fatigue, and decreased scores on Arousal and Vigor have been observed in previous studies with this drug (Johanson and Uhlenhuth, 1980a), and are consistent with the drug's known sedative properties. Decreased scores on the Anxiety subscale have not previously been observed, but are consistent with diazepam's well-known anxiolytic property. It is notable that the average baseline scores on the Anxiety subscale for the Anxious Group were almost double those for the Control Group. This difference is an independent confirmation that the subject groups differed on this dimension, since the measures used for subject selection were different. The fact that measures of anxiety were elevated both at the recruitment interview and throughout the period of the study (9-11 weeks), suggests that these subjects exhibited the "trait" of anxiety rather than a more transient "state." Scores on the ARCI for all three groups also reflect diazepam's sedative properties: PCAG ("sedative" subscale) scores were elevated and BG ("amphetamine" subscale) scores decreased.

Thus, the results from these experiments confirmed and extended earlier findings of the absence of a positive reinforcing effect of diazepam in normal human volunteers. Subjects who were anxious by DSM III criteria showed no preference for diazepam over placebo at either of the doses tested, despite this drug's measurable anxiolytic effect on the POMS. Even in a population of anxious subjects, the anti-anxiety property of the drug does not appear to be a sufficient condition to make it a positive reinforcer.

It was also shown that time of drug administration did not affect the preference for diazepam, even when the drug's presumed disruptive

effects were minimized by giving it late in the day, a time more probable for recreational drug use such as alcohol. These results contribute to the growing body of literature suggesting that diazepam is not an effective positive reinforcer in the majority of laboratory animals or humans.

It was interesting to note that the preference for amphetamine was attenuated in the two experimental groups, demonstrating that it is possible to influence choice by such manipulations, and, more importantly, that the experimental design is sensitive to alterations in reinforcement efficacy.

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Differential Effects of Diazepam and Pentobarbital on Mood and Behavior in Subjects With Histories of Sedative Drug Abuse

Roland R. Griffiths, George E. Bigelow, and Ira A. Liebson

The effects of administering moderate to high doses of diazepam (placebo, 50 mg and 100 mg) and pentobarbital (placebo, 200 mg and 400 mg) for five consecutive days to subjects with histories of sedative drug abuse were examined. The two drugs produced similar dose-related effects on psychomotor performance, daytime sleeping, and staff and subject ratings of magnitude of drug effects. Diazepam but not pentobarbital produced dose-related decreases in staff ratings of subjects' mood and social interactions, and increases in staff ratings of subjects' hostility, complaining and unusual behavior. During the ten to fourteen day placebo washout periods which followed drug administration, diazepam but not pentobarbital was associated with carryover effects on psychomotor performance, daytime sleeping and staff ratings of drug effect, mood, social interactions, hostility and confusion. The diazepam-produced deterioration in mood and social behavior observed in this study is consistent with previous case reports describing similar effects associated with chronic diazepam use in therapeutic settings.

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Rapid Physiologic Effects of Nicotine in Humans and Selective Blockade of Behavioral Effects by Mecamylamine

Jack E. Henningfield, Katsumasa Miyasato, Rolley E. Johnson, and Donald R. Jasinski

Recent research in the area of tobacco dependence has focused on characterizing the functional properties of nicotine in cigarette smoking. These studies have shown that many of the effects of cigarette smoking are due to the nicotine delivered via the smoke (Griffiths and Henningfield, 1982; Gritz, 1980). A recently completed study in our laboratory indicated that some effects of intravenous nicotine (e.g., cardiovascular and subjective responses) occurred very rapidly, onsetting within seconds and offsetting within minutes of an injection (Henningfield, Miyasato and Jasinski, 1981). That study also demonstrated that different doses of nicotine could be tested at one-hour intervals within subjects and produce reliable changes in physiologic and behavioral responses with no apparent interaction of tolerance or dose order effects.

The present report describes two experiments in which a new preparation for the analysis of rapid drug effects was utilized. In the first experiment, the temporal pattern of response to intravenous nicotine was determined in measures of skin temperature, pupil diameter, and two locations of electromyograph (EMG) recording. Selected behavioral responses were also measured. The second experiment was a replication of the first except that prior to the sessions subjects were given a dose of the centrally acting nicotinic antagonist, mecamylamine.

EXPERIMENT I. Effects of Nicotine on Physiologic and Behavioral Measures

METHOD

Subjects. The subjects were four male volunteer cigarette smokers who resided on the Clinical Pharmacology Research Unit for the approximate four-week duration of the study. Prior to the study, they were medically and psychologically evaluated, found healthy, and provided informed consent for the experimental procedures. Two subjects had histories of alcoholism (SA and

HE), one subject had taken sedatives and stimulants (BA), and one was without a history of drug dependence other than cigarette smoking (HO).

Drugs. Nicotine hydrogen tartrate was mixed with bacteriostatic saline to provide unit doses of 0.75, 1.5 and 3.0 mg (expressed as the nicotine free base). Nicotine doses or saline were delivered via an intravenous catheter placed in a forearm vein at an injection rate of 1 ml (one unit dose) per ten seconds. All drug doses were given double-blind.

Apparatus. A microcomputer-controlled physiological testing system (Cyborg) was used to collect data. Four physiologic measures collected using this system were: (1) skin temperature, taken from the index finger on the arm not equipped with a catheter; (2) two EMG measures, taken from the lower leg and the opposite forearm of that which held the catheter; (3) pupil diameter, which was measured by a closed circuit television system (from Applied Science Laboratories) and interfaced to the physiologic testing system.

Procedure. Subjects were tested individually in the morning following at least eight hours of tobacco deprivation. An experimental session consisted of four ten-minute tests which occurred at 60-minute intervals. During the ten-minute test, a subject was seated in a chair with his arms resting on a table in front of him. Every five seconds a two-second long tone was automatically turned on by the physiological testing system. During the tone the subject relaxed and focused his eyes (without blinking) on his own pupil, which was displayed on a video monitor located 150 cm in front of the subject. One second into the tone, the physiological test system simultaneously recorded the values at the EMG channels, the skin temperature channel, and the pupilometer channel. Between tone signals (3 seconds), the subject blinked his eyes 3 times. This sampling sequence continued for 10 minutes, though for the purpose of data analysis, the first two minutes of data were discarded. The intravenous dose was delivered three minutes after the start of the test, without interruption of the data collection procedure. Between these ten-minute tests, the subject was permitted to relax in another room but was not permitted to eat, smoke cigarettes or drink caffeinated beverages. Before and after tests, the subject completed structured questionnaires which measured various interoceptive (subjective) drug effects.

Experimental design. On the first test day, for each subject, placebo plus the three nicotine doses were given in order of increasing dose values. These data were not used for final analysis but the session provided an opportunity for the subject to learn and adapt to the protocol, and for the safety of the doses to be verified. Each subject was then tested for four more sessions in which all four doses were presented each session, according to a 4 x 4 latin square design across sessions. Sessions were scheduled one to three days apart.

RESULTS

Nicotine produced dose-related changes in both physiologic and behavioral measures. Figure 1 shows the bi-phasic effect of nicotine on pupil diameter. Pupil diameter began to increase during injections and further increased as a direct function of the dose level. The maximum increase was about 30 seconds post-injection and was followed by a precipitous dose-related decrease in pupil diameter. Skin temperature was decreased in a dose-related fashion in all subjects, reaching a maximum decrease within about five minutes of the nicotine injections. These decreased skin temperature levels did not recover within the 10-minute sessions. Electromyographic reponses from the lower leg were weak and were not altered in a consistent fashion by nicotine. Electromyographic responses from the upper arm occurred at much higher baseline levels and were increased by the 3.0 mg

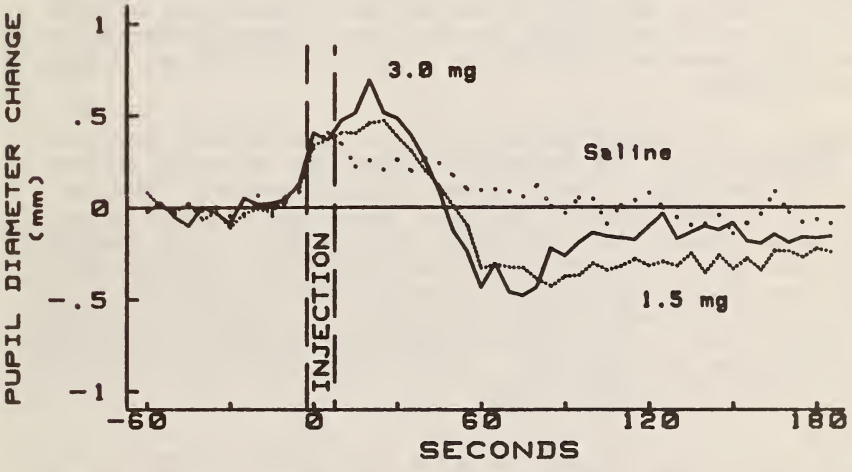

Figure 1. Mean changes in pupil diameter, from initial baseline values, are shown at three nicotine doses (n=16, 4 subjects x 4 observations). Data from the 0.75 mg dose are omitted to increase the clarity of the figure (these data were similar to those obtained at placebo). Dose levels are indicated by the label adjacent to each function.

dose of nicotine and not consistently altered by other doses of nicotine. This effect corresponded to a visibly increased muscle tension of the subjects facial and neck muscles at high nicotine doses. The most reliable subjective measure was self-reported drug dose strength which was directly increased by nicotine doses. Other self-reported responses included dose-related

increases in scores on the scale of "drug liking," and identification of the drug effects as those produced by amphetamine or cocaine (Addiction Research Center, Single Dose Questionnaire).

EXPERIMENT II. Pharmacologic Antagonism of Nicotine's Effects

METHOD

Subjects and Apparatus. These were the same as described in Experiment I.

Drugs. Nicotine doses and preparations were the same as for Experiment I. Mecamylamine doses consisted of commercially available preparations (Inversine, from Merck, Sharp and Dohme) in pill form, which were placed inside gelatin capsules with lactose filler. The doses were 2.5, 5.0 and 10.0 mg mecamylamine, and lactose placebo. All drug doses were given double-blind.

Experimental design. Each subject was tested in one four-hour session at each mecamylamine dose. The nicotine dose sequence was held constant for each subject but was varied across subjects according to a 4 x 4 latin square design. Mecamylamine doses were also presented according to a 4 x 4 latin square design across subjects.

Procedure. The general procedure was the same as that described for Experiment I. The mecamylamine dose was given 60 minutes prior to the start of the four-hour nicotine session. Additionally, 65 minutes prior to sessions, supine and standing pulse, and blood pressure were measured, along with a brief symptom check list given verbally to the subjects by the research staff with items pertaining to possible anticholinergic effects. This physical and symptomatic status evaluation was repeated at 30 and 5 minutes prior to the four-hour session, immediately following each 10-minute nicotine test, and at 1-hour intervals for three hours following the test session.

RESULTS

In the mecamylamine placebo condition, the effects of nicotine on the behavioral and physiologic variables were the same as had been measured in Experiment I. Active mecamylamine doses, however, attenuated all effects of nicotine. Figure 2 shows the mecamylamine dose-related attenuation of nicotine's effects on skin temperature. The bi-phasic effects of nicotine on pupil diameter were also eliminated by mecamylamine. Mecamylamine also attenuated the variability in EMG responses which were produced by the high nicotine dose. Whereas mecamylamine produced a dose-related attenuation of the physiological responses to nicotine, subjective responses to nicotine were maximally attentuated by the lowest mecamylamine dose. Figure 3 shows this effect most clearly in scores on the drug dose strength scale which were rated by the subjects following each 10-minute nicotine test. An orthogonol polynomials analysis confirmed that (1) mecamylamine

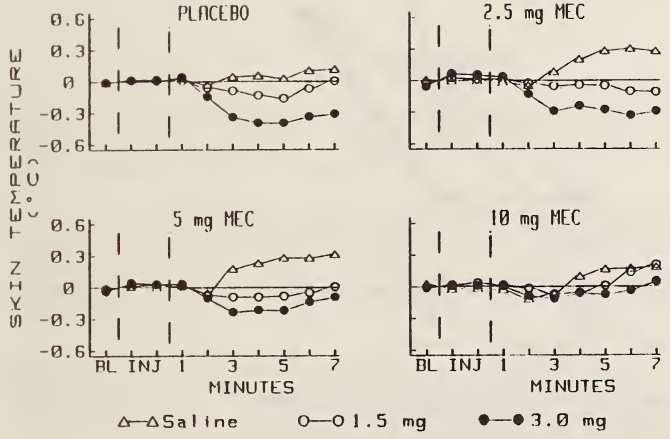

Figure 2. Mean changes in skin temperature from initial baseline values are shown as a function of nicotine dose under the four mecamylamine conditions (n=4 subjects). The values shown are those measured at each minute except for the two values measured during the injection. The 0.75 mg nicotine dose function was similar to placebo and is not shown. Open triangles indicate placebo injections; open circles indicate 1.5 mg injections; closed circles indicate 3.0 mg injections.

alone was not discriminated, (2) the slopes of the dose-strength functions were not different under the three active mecamylamine dose conditions, (3) these slopes were different from that obtained in the placebo condition, and (4) each active dose of mecamylamine produced a reliable decrease in the response to nicotine. Other subjective effects of nicotine which were observed in Experiment I and in the mecamylamine placebo condition were completely eliminated by all mecamylamine doses. These included (1) elevated drug liking scores, (2) drug identifications given as "amphetamine" and (3) the weak nicotine dose-related decreases in desire to smoke. Mecamylamine did not produce reliable changes in supine or standing blood pressure and heart rate, as determined by the physical and behavioral status examinations.

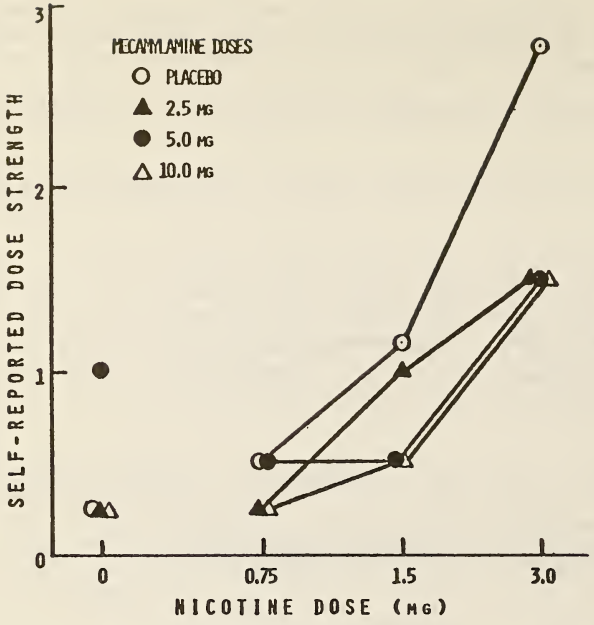

Figure 3. Post-session ratings of drug dose strength are shown as a function of nicotine dose under the four mecamylamine conditions (n=4 subjects).

DISCUSSION

This study demonstrates the utility of a new behavioral-pharmacologic preparation for the analysis of the effects of the rapid and complex activity of nicotine. Such changes in pupil diameter in response to nicotine have not been previously reported and perhaps best illustrate the sensitivity of this preparation to rapid drug effects. The pupillary response also reveals the complexity of nicotine's activity, which is a combination of sympathetic activation resulting from catecholamine release by nicotine (the nicotinic potentiation of the initial mydriasis), direct nicotinic stimulation of ganglia (the subsequent miosis), and its own self-antagonism (resulting in transient nature of the responses). The effects of nicotine on EMG responses were variable and not in the expected direction of a decrease, which would have been consistent with earlier findings by Domino that nicotine inhibited the patellar reflex (Domino, 1969). The EMG findings were, however, consistent with more recent analyses of nicotine effects on skelatal muscle activity in which it has been concluded that the effects are dependent on variables such as the measure used, the nicotine dose, and the particular muscle group under study (Domino, 1979).

The mecamylamine findings ranged from the predictable effects of apparent competitive antagonism of the nicotinic skin temperature response, to the more exciting effects of selective blockade of behavioral responses to nicotine. Specifically, the observation that mecamylamine produces a substantial blockade of subjective responses at physiologically insignificant dose levels raises the possibility that mecamylamine may provide a useful adjunct for the treatment of tobacco dependence in a similar fashion as naltrexone is used to treat opioid dependence.

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The Specificity of the Thyrotropin-Releasing Hormone (TRH) Test and Dexamethasone Suppression Test (DST) for Major Depressive Illness in Alcoholics

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It is estimated that in this country 10 million people suffer from alcoholism (1), and that the incidence of major depression in the alcoholic population ranges from 28% (2) to 59% (3). Major depression is difficult to diagnose in the presence of alcoholism because the two disorders share many signs and symptoms in common, such as sleep disorder, fatigue, anorexia, decreased libido, and apathy. Neuroendocrine abnormalities have been consistently and reproducibly demonstrated in major depression (4). The thyrotropin-releasing hormone (TRH) test and dexamethasone suppression test (DST) have a high degree of diagnostic predictive value with respect to major depression (5,6), and could aid in the diagnosis of depressed alcoholics. However, since chronic alcohol abuse also causes endocrine abnormalities directly (7), and indirectly due to coexistent hepatic dysfunction (8), the TRH test and DST abnormalities in alcoholics, when present, may be due to alcoholism per se and may not be sufficiently specific for confirming the diagnosis of major depression in this group of patients.

The effect of alcohol on the hypothalamic-pituitary-adrenal (HPA) axis is most dramatically represented by the alcohol-induced Cushingoid syndrome reported in the endocrine literature (9,10,11,12). The elevated plasma and urinary corticosteroids, abnormal circadian rhythm of plasma cortisol, and abnormal DST associated with this condition may result from alcohol-induced corticotropin release (13). Contradictory reports regarding DST testing in alcoholics include one study of 12 abstinent alcoholics showing significant non-suppression of cortisol (14) and another study of 10 alcoholics with no DST abnormalities (15). Neither studies adequately screened the alcoholics for affective disease, and the presence or absence of alcohol withdrawal was not clarified. The TRH test has been given to a small number of alcoholic patients. Loosen studied 16 chronic alcoholic men free of liver disease but with secondary depression (16). Six of 12 had a blunted TSH response to TRH during alcohol withdrawal, and 3 of 10 showed this abnormality during postwithdrawal. A more recent report showed a blunted TSH response to TRH in 3 of 15 alcoholics abstinent from alcohol for at least 2 years (17). Van Thiel studied 40 chronic

alcoholics with alcohol-induced liver disease and found the TSH responses to TRH significantly blunted when compared to normal controls (18). Alcohol administration to normals failed to produce abnormal TSH responses, and the abnormal TSH responses seen in alcoholics persisted over a 10-day period (19). Additional studies testing the TSH response to TRH have shown a delayed peak response in cirrhotic alcoholics (20) and a blunted response in alcoholics presenting with clinical signs of hyperthyroidism (21) and cirrhosis (22). It is not clear whether thyroidal abnormalities result from chronic, toxic effects of alcohol or from elements of the alcoholic life style such as poor diet or related illnesses.

In summary, relatively few studies have been reported regarding DST and TRH testing in alcoholics. None of the studies reported have tested alcoholics carefully screened for the absence of depression, liver disease, and other medical illnesses. In addition, the influence of alcohol withdrawal on the TRH test and DST has not been adequately tested by comparing pre-detoxification and post-detoxification results for these procedures. To investigate the reliability of the DST and TRH tests as confirmatory diagnostic tests for major depression in alcoholic patients, 30 consecutive admissions without liver disease, endocrine illness, or other significant medical diseases were tested with the DST and TRH test. All patients were carefully screened with a SADS-C interview (23) in order to select only patients free of RDC (24) major and minor depression, mania and hypomania. We hypothesized that we would not find abnormalities in the DST and TRH test in this group of alcoholics presenting without major depressive illness, and that this finding would indicate that these two tests are specific for major depressive illness in alcoholics. In addition, the effect of alcoholism and the alcohol withdrawal syndrome on these tests is described in order to assess the specificity of the TRH test and DST for major depression in alcoholics.

Subjects and Methods

Twenty-one male and nine female alcoholics, aged 25-57 years (38.7 $\pm$ 1.7, mean $\pm$ SEM) were studied. All patients were admitted to Fair Oaks Hospital and diagnosed as having definite alcoholism according to RDC criteria (23). None had a history of polysubstance abuse, major psychiatric illness, or previous dependence on substances other than alcohol. All patients received antibody-based testing for barbiturates, cocaine, amphetamine, opiates, marijuana and benzodiazepines in their urine at admission and none had evidence of these drugs of abuse. Patients with body weight greater than 20% over their ideal weight were excluded as were patients presenting with a present or past history of cirrhosis or hepatitis, or with a total bilirubin greater than 2.0 mg % or albumin less than 3.5 gm%. No patients were taking dilantin, coumadin, L-DOPA, bromocriptene or steroids, and none had present or past endocrine disease. Patients with anemia (Hgb < 11 gm% in females, Hgb < 13gm% in males) were excluded. Of those patients diagnosed with alcohol withdrawal syndrome, all met specific SSA criteria according to Gross, Lewis and Hasley upon admission (25). During the fourth week after admission, all patients received a SADS-C structured interview to rule out the diagnosis of RDC major or minor depressive illness, hypomanic, or manic disorder. Patients fulfilling these criteria (4 of 34 tested) were excluded from this study.

Thirteen patients fulfilling criteria for alcohol withdrawal were detoxified with chlordiazepoxide and received a TRH test and DST during the first week of admission. These tests were repeated in each of these 13 patients during the fourth week. Seventeen alcoholic patients not fulfilling criteria for alcohol withdrawal syndrome were tested only during the fourth week of hospitalization with a TRH test and a DST. Twenty normal men and woman aged 19-47 years (30.0 ± 1.9, mean ± SEM) received the TRH test. There were nine men and eleven women in this group and none had current or past major psychiatric illness. All patients and normals received the TRH test (500 mcg TRH IV) with blood drawn at 0, 15, 30, 60 and 90 minutes according to methods previously described (26). Baseline determinations of TRH, T_3 uptake, T_3 RIA and T_4 were made. All patients with a delta TSH (peak minus baseline TSH) greater than 20 uIU/ml received testing for antithyroid antibodies (27). Within three days of the TRH test, dexamethasone (1.0 mg) was administered by mouth at 12 midnight and sequential blood samples were drawn the next day at 8 a.m., 4 p.m., and midnight. The determinations of plasma cortisol levels were done in duplicate, by radioimmunoassay.

Results

In 13 of 30 alcoholics studied, thyroid parameters were measured during the withdrawal state and during the fourth week, or postwithdrawal state. These parameters, including T_3 RIA, T_4 RIA, T_3 uptake, baseline TSH and delta TSH (peak TSH minus baseline TSH) were each compared during withdrawal and postwithdrawal using a paired two-tailed Student's t-test. There were no significant differences with respect to the T_3 RIA, T_4 RIA, T_3 uptake, and baseline TSH, although there was a trend ($p < 0.10$) in T_3 RIA comparisons with greater values seen during the withdrawal state (146.5 ± 7.9, mean ± SEM) than at postwithdrawal (127.8 ± 9.0, mean ± SEM). Statistical significance ($p < 0.05$) was found comparing the delta TSH during withdrawal (7.45 ± 1.1, mean ± SEM) with the delta TSH at postwithdrawal (9.82 ± 1.9, mean ± SEM).

The thyroid measurements at week 4 in those patients showing withdrawal (N=13) were then compared using a two-tailed Student's t-test with thyroid measurements at week 4 in alcoholics not presenting with an alcohol withdrawal syndrome upon admission (N=17). There were no significant differences with respect to the T_3 RIA, T_3 uptake, baseline TSH and delta TSH. However, in alcoholics with alcohol withdrawal, the T_4 RIA at week 4 (6.85 ± 0.41, mean ± SEM) was significantly greater ($p < 0.05$) than the T_4 RIA found in alcoholics who presented with no withdrawal syndrome (5.53 ± 0.34, mean ± SEM). Since this parameter was significantly different in the two groups, the T_4 RIA values were analyzed separately with respect to normal values, whereas the fourth week values for T_3 RIA, T_3 uptake, baseline and delta TSH were combined for the two groups of alcoholics.

When the normals (N=20) were compared to the total alcoholics (N=30), a two-tailed Student's t-test showed no significant differences with respect to the T_3 RIA, T_3 uptake, baseline TSH and delta TSH. There was a large standard deviation in the alcoholics (11.74 ± 7.93, mean ± SD) compared to the normals (13.36 ± 4.36, mean ± SD) with respect to the delta TSH scores. This resulted from a bimodal distribution of delta

TSH values in the alcoholic group, in which 5 of 30 were elevated above 20 uIU/ml. In the alcoholics who presented with a withdrawal syndrome, the T_4 RIA at the fourth week (6.85 $\pm$ 0.41, mean $\pm$ SEM) was significantly less (t=3.30, $p < .01$) than the T_4 RIA seen in normals (8.7 $\pm$ 0.35, mean $\pm$ SEM). The alcoholics with no alcohol withdrawal had the smallest T_4 RIA values (5.53 $\pm$ 0.34, mean $\pm$ SEM) which were significantly less than the normal T_4 values (t=6.34, $p < 0.001$).

The delta TSH scores for the alcoholics and normals were compared with a Chi-Square test to evaluate the percentage of blunted scores (See Table 1). When a cut-off point of less than 5 uIU/ml was used to define blunting, 0 of 20 normals and 4 of 30 alcoholics at week 4 had blunted values (X^2=2.79, $p < 0.1$, NS). When a cut-off point of 7 uIU/ml was used, 8 of 30 alcoholics and 0 of 20 normals had a blunted delta TSH (X^2=6.34, $p < 0.02$), which was statistically significant. The 13 alcoholics studied during alcohol withdrawal showed 5 of 13 (38%) blunting using a cut-off of 5 uIU/ml, and 7 of 13 (54%) with a cut-off of 7 uIU/ml. Both of these findings were highly significant when compared to the normals (X^2=11.64, $p < .001$ and X^2=7.52, $p < .01$ respectively). We have defined augmented responses as a delta TSH greater than 20 uIU/ml. Five of 30 alcoholics (17%) and 1 of 20 normals (5%) showed a delta TSH greater than 20 IU/ml. This finding was not statistically significant.

	Normals (N=20)	Toxic Alcoholics (N=13)	Detoxified Alcoholics (N=30)
Percent Blunted delta TSH scores (cut-off=5uIU/ml)	0%	38%($p < 0.001$)	13%(NS)
Percent Blunted delta TSH score (cut-off=7uIU/ml)	0%	54%($p < 0.01$)	27%($p < 0.02$)

Table 1. Percent of blunted delta TSH responses in normals, toxic alcoholics, and detoxified alcoholics according to defined cut-off points of 5uIU/ml and 7uIU/ml.

With the DST, cortisol values were analyzed at 8 a.m., 4 p.m., and 12 midnight as described. Since Carroll's work has defined normal values for this test (6), a control group was not obtained. An abnormal DST was defined as any cortisol value after 1.0 mg dexamethasone greater than 5 ug/dL. At 4 weeks, none of the 30 alcoholics had an abnormal DST. The alcoholics studied during alcohol withdrawal showed abnormalities on the DST in 2 of 13 cases. There were no baseline cortisol differences in the alcoholics during withdrawal as compared to baseline cortisol during the fourth week.

Discussion

The data presented here indicate that, in alcoholics screened for the absence of affective disease, hepatic dysfunction and other medical illnesses, there are neuroendocrine abnormalities relevent to the use of current confirmatory laboratory tests for major depression. With respect to the TRH test, this refutes our hypothesis that no abnormalities would be present in this group of alcoholics devoid of major depression. Our hypothesis was supported by the DST data showing no abnormalities in detoxified non-depressed alcoholics. The test re-test data indicate that the neuroendocrine effects of alcoholism tend to be most pronounced during the alcohol withdrawal state, especially in the thyroid axis. This finding is largely in agreement with previous reports (16,18) but with these data it has now been shown to be more clearly related to alcoholism than concomitant depression or liver disease. The degree of blunting with the TRH test implies that it is an unsuitable test for depression in alcoholics, particularly if administered during a period of alcohol withdrawal. Even during the fourth week after detoxification there was an unusually high frequency of inadequate responses, both by the stringent criterion of 5 uIU/ml and the more sensitive criterion of 7 uIU/ml as a cut-off point for a blunted delta TSH response. This has implications regarding the significance of a blunted delta TSH in a clinical situation. The diagnosis of alcoholism is often missed because of the strong denial associated with the disease. The presence of a blunted TRH test, in the absence of a clinical picture of depression, should alert the physician to the possibility of alcoholism and indicate the desirability of contacting a family or close friend informant in order to explore this possibility.

Our findings demonstrate significantly higher T_4 values during withdrawal than at postwithdrawal. This has been reported previously (28) and attributed to relatively increased thyroidal activation during alcohol withdrawal, in which certain clinical signs and symptoms resemble hyperthyroidism (21). The finding that T_4 levels are lower in both toxic and postwithdrawal alcoholics than in normals has also been reported (7), although not universally (16). This finding may represent a direct toxic effect of alcohol on the thyroid gland and is supported by our finding that 5 of 30 alcoholics actually had augmented TSH responses to TRH, perhaps compensating for a mildly hypoactive thyroid gland. None of these 5 patients had antithyroid antibodies in their blood which might have explained their augmented TSH responses. Perhaps alcohol exerts toxic effects, depending on dose and duration, on both the thyroid gland (leading to decreased thyroxin and an increased TSH response to TRH) and on the hypothalamic-pituitary segment of the thyroid axis, leading to blunted TSH responses. The degree of thyroid abnormalities in alcoholics seen during the first few weeks after cessation of drinking indicates that assessment of their thyroid status with the TRH test may be an important adjunct in their evaluation and treatment. This possibility requires further study.

The DST data is very encouraging from a diagnostic point of view. Negative findings for all 30 of 30 alcoholics during the fourth week offer strong support for the hypothesis that the DST is specific for major depression and devoid of false positives related to alcoholism in detoxified

alcoholics. Our finding that 2 of 13 alcoholics in acute withdrawal had an abnormal DST result implies that the clinician should conduct the DST during the alcohol withdrawal state with caution and repeat any positive findings at a later time. These data with the DST support the efficacy of more widespread use of this excellent and practical laboratory test for depression in the high risk alcoholic population. Further research is currently underway at Fair Oaks Hospital to test the predictive value of the DST in identifying alcoholics meeting RDC criteria for major depression.

In conclusion, the DST appears to be an excellent diagnostic test for confirming the diagnosis of major depression in the alcoholic population. This easily administered test might serve as an effective screen for depression in certain alcoholic patients who are at considerable risk for this psychiatric disorder. Neuroendocrine testing with the DST may identify patients who are self-medicating their psychiatric illness with alcohol, or who prefer the diagnosis of alcoholism to that of major depressive illness. The TRH test, however, lacks specificity for depression in alcoholics, and is especially abnormal during acute alcohol withdrawal. In fact, a blunted TSH response to TRH in an individual lacking a clinical picture of depression should raise the clinician's index of suspicion for alcoholism. Further use of appropriate neuroendocrine tests for the diagnosis of psychiatric disorders should enable alcoholic patients requiring psychiatric treatment to be more easily identified and treated.

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The Symptoms of Alcohol Withdrawal as Predictors of Behavioral and Physiological Responses to an Ethanol Stimulus

Richard F. Kaplan, Roger E. Meyer, and Charles F. Stroebel

INTRODUCTION

Behavioral and psychophysiological studies of alcoholism have tended to "lump" alcoholics into a specific group, despite the fact that behavioral theory would suggest that individuals will differ in their operant and physiological response to ethanol as a function of prior reinforcement history. Edwards and Gross (1976) sought to describe the elements of a "behavioral syndrome" which could be differentiated from alcohol-related disabilities. They attempted to define criteria which emphasized the elements of "dependence" that could be quantified across a continuum of severity. When Hershon (1977) examined two elements of Edwards' dependence syndrome, withdrawal symptoms and drinking to relieve these symptoms, he found a positive correlation between withdrawal symptomatology and drinking behavior in 100 alcoholic patients. More recently, Hesselbrock et al. (1981) positively correlated withdrawal symptomatology in the last 30 days and frequency of alcohol consumption in 114 alcoholic patients. These studies in two different samples of alcoholics strongly suggest the utility of examining elements of alcohol dependence along a continuum of severity.

For behavioral researchers, the definition of a behavioral syndrome which can be studied in the laboratory should permit comparison of the stimulus control of psychophysiological and behavioral responses to ethanol (and stimuli associated with ethanol) between subjects. Since a history of ethanol dependence can affect the respondent, discriminative, and reinforcing stimulus properties of ethanol within the subject, an examination of the syndrome in the laboratory should include the assessment of physiological, subjective, and operant responses in subjects who differ in the severity of the alcohol dependence syndrome.

The present study is an attempt to investigate the contributions of subclinical withdrawal symptomatology occurring in the previous 30 days to psychophysiological

arousal, desire to drink, and operant behavior associated with alcohol within the clinical laboratory. The methodology incorporates the monitoring of psychophysiological responding and subjective desire to drink with the opportunity to work for a drink reward.

MATERIALS AND METHODS

Subjects

The subjects were 16 alcoholic patients (mean age 33.67) recruited from the inpatient Alcohol Treatment Unit at the University of Connecticut Health Center and 16 control subjects (mean age 28.0) selected from responses to posted advertisements. All alcoholic subjects had a history of heavy drinking of at least five years (mean years = 15.1 years). All controls rated themselves as social drinkers who drank beer.

Questionnaires

The present report focuses on a self-report instrument called the "Last 30 Days of Drinking Questionnaire," which concentrates on withdrawal symptoms and drinking behavior during the month just prior to hospital admission. Items in the first part of this questionnaire were developed by Hershon (1977) to measure withdrawal symptomatology, particularly in the areas of physiological discomfort and affective disturbance. Each item was rated on a four-point Likert-type scale representing frequency of occurrence in the last month of drinking. The response categories ranged from "never" to "everyday." The second part of the survey presented a series of items measuring the quantity and frequency of wine, beer, and liquor consumption.

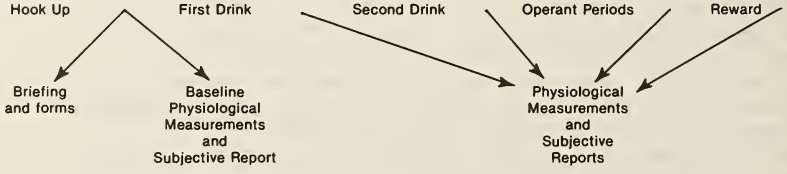
Procedure

Subjects in both the alcoholic and control groups were randomly assigned on a double blind basis to either an ethanol or placebo condition at the start of the experiment.

The sequence of events is summarized in Table 1. All subjects were studied individually. At the outset of the experimental period, each subject was seated in a comfortable chair. Sensors for measuring heart rate, skin conductance, and finger temperature were connected. Each subject was then given a variety of questionnaires to complete; which also allowed time for stabilization of physiological responses.

TABLE 1

Experimental Design



The beer or non-ethanol containing malt beverage was presented to the subjects in a frosted mug on a tray which also

held an empty can of a commercially available alcoholic brand of beer. The subjects were asked to hold, smell, and think about the drink for one minute while physiological measurements were being taken. At the end of the minute each subject was asked to record (1) his desire for a beer (no desire to greatest desire), (2) his belief whether the beer actually contained alcohol (definitely contains alcohol to definitely does not contain alcohol), and (3) his subjective response to the beer (non-intoxicated to intoxicated). After the minute of psychophysiological assessment and subjective report, each subject was given five minutes to consume the drink. After consumption of the first drink, a second drink identical to the first was presented and consumed following this same procedure. Subjects were then instructed that they had an opportunity to work for a third drink identical to the first two, or a Connecticut state lottery ticket (whichever they chose). The procedure for obtaining the reward consisted of a progressive-ratio operant task as described by Funderburk and Allen (1977). When sufficient points had been accumulated to secure the reinforcer, subjects were again told that they could have a third drink or the lottery ticket.

RESULTS

Alcohol Dependence Syndrome

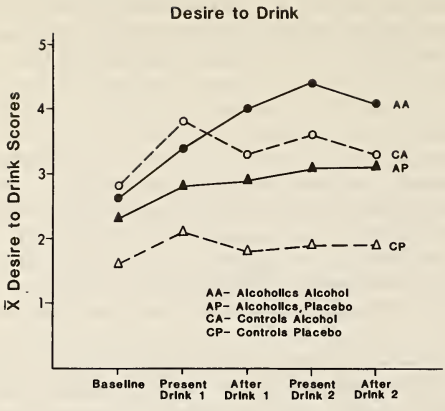
The mean scores on the Last 30 Days of Drinking Questionnaire for the groups: alcoholics receiving alcohol (AA), alcoholics receiving placebo (AP), controls receiving alcohol (CA), and controls receiving placebo (CP) were 57.75, 65.24, 38.75 and 40.29 respectively. A one-way ANOVA indicated significant group differences ($F=9.32$, $df=3.28$, $p<.001$); and the Newman-Keuls comparison showed that both alcoholic groups were significantly more dependent than either control group; alcoholic groups did not differ from each other and neither did control groups differ from each other.

Desire to Drink

The desire to drink scores were analyzed using a split-plot analysis of variance with groups as the between subjects factor, and time point in the experiment as the within subjects factor. Where significant main effects were found, mean comparisons were computed using the Newman-Keuls test for multiple comparisons.

All groups increased their desire to drink level upon presentation and before the consumption of the first drink. The alcoholic group receiving alcohol (AA group) showed a significantly higher desire to drink level following consumption of the first drink than all other groups ($p<.05$). The AA group maintained this difference (Figure 1) throughout the experimental period. Both the AP and CA groups manifested significantly greater desire to drink than the CP group ($p<.05$).

FIGURE 1



It is of special interest that 6 of 8 alcoholics (after 2 drinks) who received placebo thought that they had received real beer; whereas only 2 of 8 control subjects receiving placebo thought that the placebo drink was real beer. These data which can be seen in Table 2 were analyzed using the χ^2 statistic and were significant at $p<.05$. Moreover, there was a

TABLE 2

Do You Think the Drinks You Had Contained Alcohol?

	Alcoholics		Controls	
	Beer	Placebo	Beer	Placebo
Yes	6	6	7	2
No or Not Sure	2	2	1	6

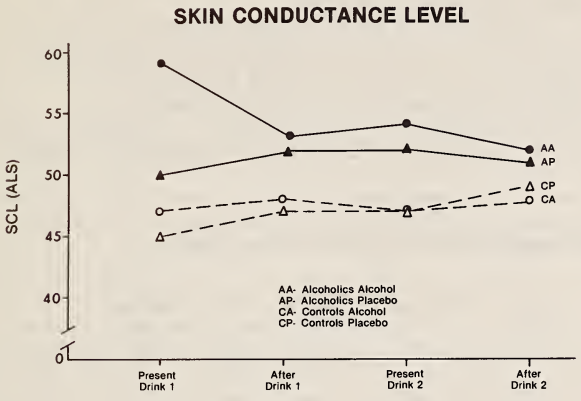
positive correlation between the assumption that the placebo was real beer and the alcoholics' increase in desire to drink following consumption of the first beer (rho=0.63, $p<.045$). This correlation was also significant for the AA group (rho=0.73, $p<.01$); but not for either control group. Finally, the correlation between severity of alcohol dependence in the alcoholic subjects and the rating of placebo as real beer approached statistical significance (rho=0.41, $p<.056$).

Physiological Responses

SCL scores were transformed using Lacey's (1966) autonomic lability score (ALS) formula to compensate for baseline differences and the law of initial values. As can be seen in Figure 2 both alcoholic groups showed a greater SCL response

to the presentation of the first drink. This was statistically significant only for the alcoholic group that received alcohol ($p<.05$).

FIGURE 2



There was also a significant correlation between SCL (ALS) to the initial presentation of the beverage (before consumption) and increased desire to drink in the combined group of alcoholic subjects ($r=.46$, $p<.04$) (AA and AP); but not in control subjects. There was a positive correlation between SCL response to the drink prior to consumption and severity of alcohol dependence in the AA group ($rho=.58$, $p<.06$) suggesting some effect of alcohol dependence on psychophysiological arousal to stimuli associated with drinking. This was not, however, seen in our other alcohol group or either control group. The two groups of alcoholic subjects and the control subjects who received real beer also manifested a small increase in heart rate with the presentation of the first drink. Following consumption of this drink, heart rate dropped in all groups. It increased in the AA group following presentation of the second drink and remained elevated in this group through the remainder of the experiment.

There were no significant differences between group means for skin temperature and there were no differences across the time points in the experiment for this variable.

Operant Responding and Reward Choice

There was no significant differences between groups in accumulated operant points. All but one subject earned sufficient points to receive either the drink or the lottery ticket by at least the end of the second operant period. This one alcoholic subject in the AP group refused to press the operant button and was not included in this analysis.

Although the operant task did not discriminate among our groups, reward choice of beer or lottery ticket did. Within the AA and AP groups half of the subjects chose the drink

reward and half chose the lottery ticket. Five of the subjects in CA group chose the drink but only 2 of 8 subjects in the CP group picked the drink. Among the alcoholic subjects (but not among the controls) there was a significant correlation between thinking that a drink contained real beer and the decision to choose the drink reward (rho=.46, $p<.04$).

In an attempt to examine those variables affecting the choice of the drink reward within each population (alcoholics and controls) we computed a forward stepwise multiple regression with alcohol dependence, increase in desire to drink, whether or not the subject received beer or placebo, and our psychophysiological measures as predictor variables. Table

TABLE 3

Multiple Regression Analysis: Prediction of Beer Reward

Predictor Variable	R Square	RSQ Change	Simple R	F	Significance
Increased Desire	.27	.27	.52	4.22	.05
Withdrawal Symptoms	.44	.16	.50	5.33	.05
Heart Rate Increase	.57	.13	.38	3.71	.05

Multiple R = .76

3 shows that for our alcoholic population, an increase in desire to drink, a higher degree of alcohol dependence and an increase in cardiac rate to the presentation of the drink all contributed significantly in predicting choice of drink reward. These three variables accounted for over 57% of the total variance. It is important to point out that whether the alcoholic received real beer or placebo did not significantly predict choice of reward. For our control non-alcoholic beer drinking subjects, only desire to drink significantly contributed as a predictor of reward choice.

DISCUSSION

The major finding in the present study is that for alcoholic subjects severity of alcohol dependence, increased desire to drink, and increased heart rate in response to alcohol-associated stimuli all significantly contributed to the probability that a subject would select and consume an optional drink. This did not occur within the control population for whom only an increased desire to drink significantly predicted choice and consumption of the drink reward. Also, an increase in desire to drink among alcoholic subjects was significantly related to their belief that they were actually drinking real beer in both the beer and placebo groups. This is consistent with the data of Meyer and Mirin that describes craving in the heroin addict as greatest in situations in which he expects to consume heroin (Meyer & Mirin, 1979). It is also consistent with the data of Marlatt and Rohsenow who demonstrated that the

expectation that alcohol is being consumed is more important than actual alcohol content in predicting drinking behavior in the alcoholic (Marlatt & Rohsenow, 1980). We believe that the placebo response in our alcohol group, which was not apparent in control subjects, is evidence of conditioned discriminative effects in the alcoholic. That this also predicted the choice of reinforcer (the placebo beverage in preference to the lottery ticket) in the alcoholic subjects is suggestive evidence of conditioned reinforcement in individuals with a history of alcohol dependence. Since the correlation between severity of alcohol dependence and our physiological variable of SCL only approached significance in one of our alcoholic groups (AA), we suspect this relationship is more complex. It is possible that respondent conditioning may be manifested more clearly with other physiological or neuroendocrine measures that we did not measure. It is also likely that severity of alcohol dependence in the last 30 days of drinking does not account for all aspects of reinforcement history.

Finally, the data confirm the caveat of Hodgson, Rankin, and Stockwell (1979) that studies of "craving" in the alcoholic in the laboratory should view it as a multidimentional phenomenon. Our findings suggest that severity of alcohol dependence, increased arousal (as manifested by increased heart rate) and increased desire to drink in response to ethanol independently increased our ability to predict the choice of a third drink. We thus believe that physiological and subjective data add an important dimension which is critical to studying the three conditioned alcohol stimulus properties consequent to prior ethanol consumption. Further work is needed to establish the validity of the alcohol dependence syndrome in the laboratory in order to establish its usefulness in differentiating among alcoholics in clinical settings.

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Due to space limitations, a complete list of references may be obtained from the senior author.

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Initial Opiate Use and Treatment Outcome in Methadone Detoxification Patients

Mary E. McCaul, Maxine L. Stitzer, George E. Bigelow, and Ira A. Liebson

Overall rates of illicit opiate use are frequently quite high among opiate-dependent patients during outpatient methadone detoxification treatment (Fulwiler et al. 1979; Hall et al. 1979; Sorensen et al. 1982; Wilson et al. 1974). We have noticed, however, that individual street addict patients may differ markedly in rate of opiate-positive urinalysis results during the initial weeks of their enrollment in a 90-day outpatient methadone detoxification program. Some patients show continuous opiate positive tests after enrolling in treatment, while others are virtually opiate free early in treatment. These different patterns of drug use suggest a higher degree of treatment motivation among patients with very low initial rates of urine positives.

The present paper compares two groups of detoxification patients who differed on initial levels of opiate use, as revealed in urinalysis test results. The first purpose of this comparison was to identify any additional demographic or behavioral characteristics which might differentiate patients who exhibit very different levels of involvement with opiate use early in outpatient detoxification treatment. The second purpose was to determine whether treatment prognosis was any better for patients who showed little or no opiate use early in detoxification treatment compared to patients who showed persistent opiate use at the beginning of treatment.

Methods

This paper reports data for 20 of the 55 male patients who entered 90-day outpatient detoxification treatment at the Behavioral Pharmacology Research Unit of Baltimore City Hospitals during a 12-month period of time. Eligibility for treatment was based upon urinalysis evidence of recent opiate use obtained at the initial contact with the program. All detoxification enrollees were classified into two groups on the basis of the number of morphine-positive tests observed in four urine samples collected during the second and third weeks of enrollment.

Patients with three or more morphine-positive tests were classified as high frequency opiate users (32.7 percent of enrollees) while patients with two or fewer morphine-positive urine samples were classified as low frequency opiate users (67.3 percent of enrollees). Patients of each type were randomly assigned either to a behavioral intervention condition (data to be reported elsewhere) or to a control condition. The present paper reports comparative data for the first ten consecutive enrollees classified into the high and low frequency opiate positive groups and assigned to control detoxification treatment.

Baseline measures. Demographic data were obtained from patient self-report during a clinical intake interview conducted prior to treatment enrollment. Demographic variables reported are shown in Table 1. Four behavioral measures were examined during weeks 2 and 3 of treatment enrollment, when all patients were maintained on 30 mg/day of methadone: 1) Morphine-positive urine tests. Urine samples were collected twice weekly on Mondays and Fridays. Samples were tested for presence of morphine using an onsite EMIT system (Syva Corp.). 2) Clinic attendance. Missed clinic appointments ("no shows") were calculated as the percent of opportunities to attend based upon the number of patients enrolled in treatment. 3) Sedative positives. One of the two urine samples collected each week was randomly selected for testing at an outside laboratory by thin layer chromatography analysis. Data reported for sedative drugs include benzodiazepines, unspecified barbiturates, phenobarbital, methaqualone, amitriptyline and phenothiazines. Each urine sample could contribute only a single sedative positive result to the weekly percent of positive specimens even if multiple sedative drugs were identified. Missing urine samples did not contribute to this analysis. 4) Symptom reports. Subjects completed a 60-item symptomatology checklist twice weekly (Mondays and Fridays) on which they reported any symptoms experienced during the previous 24 hours and rated severity of the symptoms on a scale of 0 - 4. The checklist contained a variety of symptoms specific to opiate withdrawal as well as a wide range of miscellaneous complaints. A total score was calculated by adding together the severity score for each item marked by the patient.

Detoxification procedures. All patients were stabilized for 21 days on a dose of 30 mg/day methadone. Both groups also were detoxified according to a blind gradual 6-week dose reduction schedule followed by maintenance on cherry syrup vehicle. However, for the high frequency opiate group, stabilization at 30 mg was followed by an increase to a 50 mg dose for 14 days then a return to 30 mg for an additional week prior to dose reduction. The rationale for this dose increase was to improve the prognosis for this group by allowing subjects additional time to reduce their supplemental opiate use prior to initiating the dose reduction procedure. As a consequence, the high frequency opiate group received their dose reductions three weeks later in the detoxification protocol than did the low frequency opiate group and received placebo methadone (vehicle only) for a shorter time

(one week as compared to three weeks).

Detoxification outcome comparison. The outcome measure used for comparison between the two groups was percent of opiate (morphine) positive urinalysis tests observed during the 90 day detoxification program. Urine samples were collected and analyzed twice weekly. Missing samples were counted as morphine-positive as long as the patient remained in treatment. Once a patient terminated treatment he no longer contributed to urinalysis results. Because the groups were exposed to different dosage schedules, data are reported for the two groups at comparable dose levels rather than at comparable times during the detoxification protocol. Data for the high frequency opiate group are shown for the entire 90-day period, while data for the low frequency group include only the first week of placebo methadone treatment.

Results

Baseline Characteristics

Demographic variables. As shown in Table 1, demographic characteristics of the high and low frequency opiate users were quite similar in terms of age, racial group and history of opiate use. The high frequency opiate group had more patients who were currently involved with the criminal justice system, a somewhat higher rate of currently unemployed patients and fewer high school graduates than the low frequency opiate group. However, these differences were not statistically significant.

Behavioral variables. During baseline stabilization, 92.5 percent of urine samples were morphine-positive for the high frequency opiate group while 7.5 percent of samples were morphine-positive for the low frequency opiate group. Regularity of clinic attendance also differed for the two groups of patients during the baseline stabilization period. During this time, the low frequency opiate users never missed any scheduled clinic appointments, while the high frequency users missed about 10 percent of scheduled appointments. The two groups did not differ either on their use of sedative drugs or on reported levels of symptomatology during the baseline portion of the study. Both groups showed about 22 percent of tests positive for sedative drugs, these being primarily benzodiazepine-positive tests.

Detoxification outcome. As shown in Figure 1, opiate positive samples for the low frequency group increased steadily during the detoxification, reaching 60 percent positive samples during the period when dosage was between 8 mg and 0 mg (study weeks 9 - 11). One patient remained opiate-free throughout the dose reduction period; all the rest showed a substantial number of opiate positive specimens. Despite this gradual increase in urine-positive results, the low frequency group did maintain superiority over the high frequency opiate group throughout the detoxification program. For the high frequency opiate group, the percent of urine positive tests was lowest during the time that their dose

TABLE 1. *Characteristics of Detoxification Patients*

	Low Frequency Opiate Group (N=10)	High Frequency Opiate Group (N=10)
Demographic Variables		
Average age (yrs) (± SD)	29.4 (3.5)	30.6 (5.7)
Race (%)		
black	50	50
white	50	50
Average years of continuous opiate use (range)	8 - 1 (2 - 12)	10 - 1 (2 - 18)
Legal status (%)		
free	70	50
free pending trial	-	30
parole/probation	30	20
Currently employed (%)	30	60
Education		
average years completed (± SD)	10.8 (2.4)	10.1 (2.7)
Percent of patients completing		
no high school	40	30
some high school	-	50
high school graduate or more	60	20
Behavioral Variables		
Morphine-positive urines (%)	7.5	92.5
Sedative-positive urines (%)	22.2	21.4
Missed clinic appointments (%)	0.0	10.0
Average symptomatology score	20.5	24.0

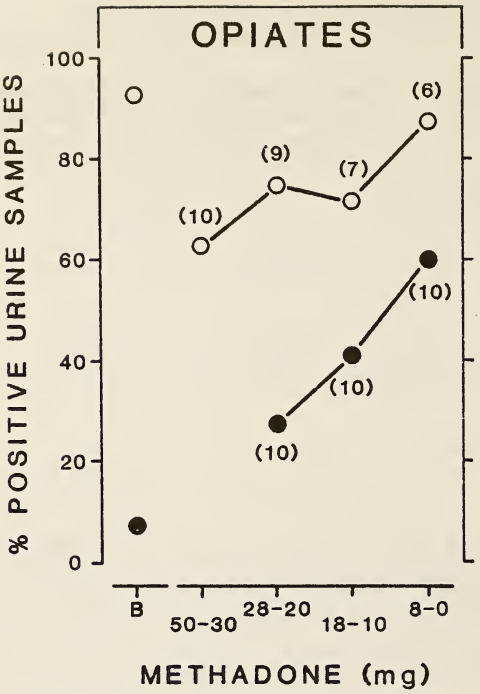

FIG. 1. *Percent morphine-positive urine samples during methadone detoxification for subjects with high (open circles) and low (closed circles) rates of opiate-positive urine samples during an initial two week period of dosage stabilization (B). Shown in parentheses are the number of patients remaining in treatment at each dosage reduction level.*

increased to 50 mg methadone, with 62.5 percent of samples morphine-positive. By the end of treatment, the opiate positive rate for this group had returned to initial baseline levels, with 87.5 percent positive samples.

Discussion

Although there was a clear and dramatic difference in rates of opiate-positive urine results observed between two groups of patients during the initial baseline stabilization portion of a 90-day outpatient methadone detoxification treatment program, the data presented in this paper generally support the conclusion that these two groups of patients did not differ either in their pretreatment demographic characteristics or in other relevant pretreatment behaviors including use of sedative drugs. Some interesting trends were noted in the demographic data including more criminal involvement among the high frequency opiate users and more formal education in the low frequency opiate users. The

fact that employment rate was higher among subjects who used supplemental opiate drugs runs counter to the popular belief that excessive drug use is associated with unemployment.

Regularity of clinic attendance did differentiate the two groups. The groups which used more opiate drugs had more irregular clinic attendance, although the absolute rate of missed appointments was relatively low (10 percent). The nature of the relationship between these two behavioral measures is not clear. Patients may have been using more opiates to relieve withdrawal symptoms resulting from missed methadone doses. Alternatively, patients may have missed methadone doses in order to enhance the effects of supplemental opiates which they planned on taking. Finally, the two measures may have no causal relationship but both may reflect a common underlying lack of treatment motivation. Additional evidence for a relative lack of treatment motivation among patients in the high frequency opiate group may be reflected in the fact that three of these patients were terminated from treatment by clinic staff prior to the end of their 90 day enrollment for failure to comply with various clinic regulations.

The dose increase manipulation appeared to have a beneficial impact on supplemental drug use in the high frequency opiate users. Opiate-positive samples were reduced by about 30 percent during the dose increase manipulation compared to rates observed during the previous two-week baseline dose stabilization period. These effects were only temporary, of course, since drug use again increased during gradual dose reduction and detoxification.

The fact that some patients stop or drastically curtail their street use of opiates and adhere strictly to the prescribed treatment regimen during the early stages of methadone detoxification treatment suggests that these patients are initially well motivated for treatment. These patients continued to maintain superior rates of opiate-free urines during the detoxification compared to patients who initially showed a high rate of illicit opiate use. However, the present comparison study suggests that the ultimate prognosis in terms of continued illicit opiate use is equally poor both for patients who do and do not give up their supplemental opiate use during the initial portions of detoxification treatment.

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Motoric and Attentional Behavior in Infants of Methadone-Maintained Women

Sydney L. Hans and Joseph Marcus

The effects of in utero exposure to opiates on the neonate have been well documented in the research literature (Finnegan et al. 1975, Kron et al. 1975, Lodge et al. 1975, Rosen and Pippenger 1976, Strauss et al. 1975). Neuro-behavioral manifestations of neonatal narcotic abstinence syndrome include hypertonicity, tremulousness, jerky motor movements, weak sucking, frantic hand-to-mouth movements, and high-pitched crying. In particular, the neonatal effects of exposure to drugs seem to be most pronounced and long lasting in the area of motoric functioning (Marcus et al. 1982a & b).

There are few reports on the behavior of offspring of drug-using women past the neonatal period. These studies have generally used standardized tests of infant skill acquisition that are summarized by developmental quotients analogous to adult IQ scores. In virtually all studies, these measures have failed to show differences between drug-exposed and control infants (Strauss et al. 1976, Chasnoff et al. 1980, Wilson et al. 1973, Strauss et al. 1979, Ramer and Lodge 1975, Kaltenback et al. 1979; Johnson and Rosen 1981, Wilson et al. 1981).

The few findings of post-neonatal differences between opiate-exposed and other infants have been from those studies employing clinical measures or scales that rate qualitative aspects of behavior rather than rate of skill acquisition--scales that measure how a skill is performed rather than whether it is performed. Lodge (1978) observed that methadone toddlers were highly energetic, active, reactive to stimuli, and easily distractible; their overall persistence, attention span and goal-directedness were brief. Wilson et al. (1981) described them as less attentive and more active than comparison infants. Strauss et al. (1979) reported that methadone group 5-year-olds showed higher gross bodily movement, higher energy level, poorer fine-motor coordination, and more irrelevant minor movements than other children. Wilson et al. (1979) reported that at preschool and school age, a group of narcotic-exposed children showed deficits in perception, quantitative skills, and memory. Their parents described them as impulsive, difficult, aggressive, and lacking self-control.

The particular symptoms that are emerging from different studies as characteristics of drug-exposed children are not a random set of

behaviors. They are typical of the symptoms of Attention Deficit Disorder (ADD). As described by the most recent Diagnostic and Statistical Manual of the American Psychiatric Association (APA 1980), the essential features of ADD (also referred to as minimal brain dysfunction and the hyperkinetic child syndrome) are short attention span and poor concentration. Associated with the syndrome in some cases are impulsivity, excessive motor activity, negativism, impaired academic performance and neurological soft signs such as clumsiness. Little is known about the early etiology of ADD since it is generally not observed until a child is placed in the constraints of a classroom setting, although parents have reported that their ADD children began showing symptoms even during infancy (Stewart et al. 1966, Werry et al. 1964).

The purpose of the present paper is to report on longitudinal assessments made of 4- and 12-month-old infants of methadone-maintained women using the Bayley Scales of Infant Development. Analyses will look for differences in developmental quotients and also differences in qualitative aspects of behavior as assessed by the Infant Behavior Record (IBR) part of the Bayley Scales. The IBR will be analyzed to look for differences in ADD-type behaviors between individual methadone and comparison children and to examine temporal patterns in the development of such behaviors.

METHOD

Subjects

Infants were the first cohort (N=45) of subjects in a longitudinal study on the effects of in utero methadone exposure on child development. The sample was composed of a group of black infants whose mothers were being treated in methadone maintenance programs on the south side of Chicago and a comparison group whose mothers were of similar age and socioeconomic background, but had no history of drug-use or alcohol abuse. In previous papers, we have reported on the behavior of these infants during the first month of life as assessed by the Brazelton Neonatal Assessment Scale (Brazelton 1973, Horowitz et al. 1978). During this period the offspring of the methadone mothers showed marked abnormalities in motor functioning including hypertonicity, tremulousness, and poor motor maturity. There was a subgroup of the methadone infants who also showed poor state functioning; specifically, poor alertness and high irritability (Marcus et al. 1982a).

The present paper reports data on the 39 infants in this cohort who were assessed at both 4- and 12-months of age: 16 from the methadone group and 23 from the comparison group. Six infants from the original cohort were not included due to sudden infant death (1 methadone group female), serious brain damage from a stroke (1 methadone group male), unavailability for testing at the 4-month age only (1 methadone group female and 1 comparison group male), unavailability for testing at the 12-month age only (1 methadone group female), and mother's withdrawal of consent after the neonatal period (1 comparison group female).

Procedures

Mothers and infants were brought for assessment to laboratories at the University of Chicago. Following a 25-minute videotaping session, infants were seated in the mothers' laps and administered the Bayley Scales of Infant Development (Bayley 1969) by a trained female examiner. Examiners did not know whether infants were part of the methadone or comparison group, and they did not have access to information about infants' behavior at earlier ages.

DATA ANALYSIS

The Bayley IBR consists of 35 items rated on 2-, 5-, and 9- point scales by the examiner at completion of the examination. Items on the IBR measure at least three of the symptoms observed in ADD: poor attention span, high activity level, and poor motor coordination. Three psychologists were asked to nominate items from the IBR that they thought were examples of these types of functioning. From this item pool, items representing the three symptoms were selected according to the following criteria: that all items within a category were monotonically related to one another both within the methadone and comparison groups and at both 4- and 12-months. On this basis the following items were selected to represent each category: ATTENTION--Responsiveness to Objects (#8), Goal Directedness (#11), Attention Span (#12), and Reactivity (#15); ACTIVITY LEVEL--Activity (#14) and Energy (#25); and MOTOR COORDINATION--Gross Motor Coordination (#26) and Fine Motor Coordination (#27).

In order to look at the structural relationships of these variables, Partial Order Scalogram Analysis with Base Coordinates (POSAC) (Shye 1980) was performed in two dimensions using an input profile for each child of these eight IBR variables as assessed at 4-months of age. In this analysis, the energy items showed no clear regionality and the POSAC was recomputed using an input profile of only the four attention and two motor coordination items. The resulting two dimensional space is displayed in Figure 1. The POSAC arranges subjects in space along a joint direction with the most poorly functioning infants at the lower left and the best functioning infants at the upper right. The base axes in this POSAC represented the attention items (on the horizontal axis) and the motor coordination items (on the vertical axis). In this figure, methadone group infants are indicated by circles; comparison group infants by squares. The POSAC space reveals strong discrimination between the methadone and comparison groups, with those showing poorest motor coordination being almost exclusively methadone infants. A dotted line on the figure highlights this subgroup of poorer functioning infants. It consists of 7 methadone group infants and only one comparison group infant.

A similar POSAC was computed on the attention and motor coordination profiles at 12 months of age. Again, in the resulting space, the two axes represented attention and motor coordination. See Figure 2. The resulting configuration shows sharp discrimination between methadone and comparison group infants. At this age, however, the

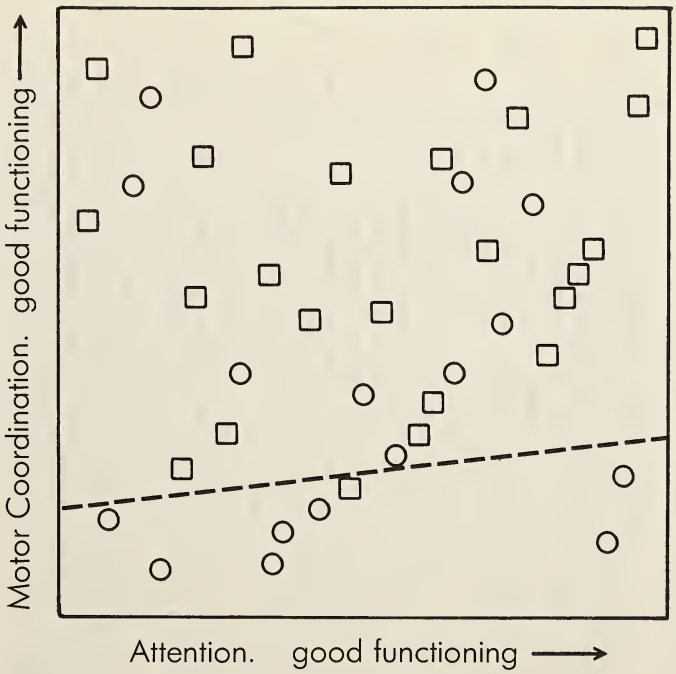

FIGURE 1. POSAC of 4-Month IBR Items.

○ = Methadone. □ = Comparison.

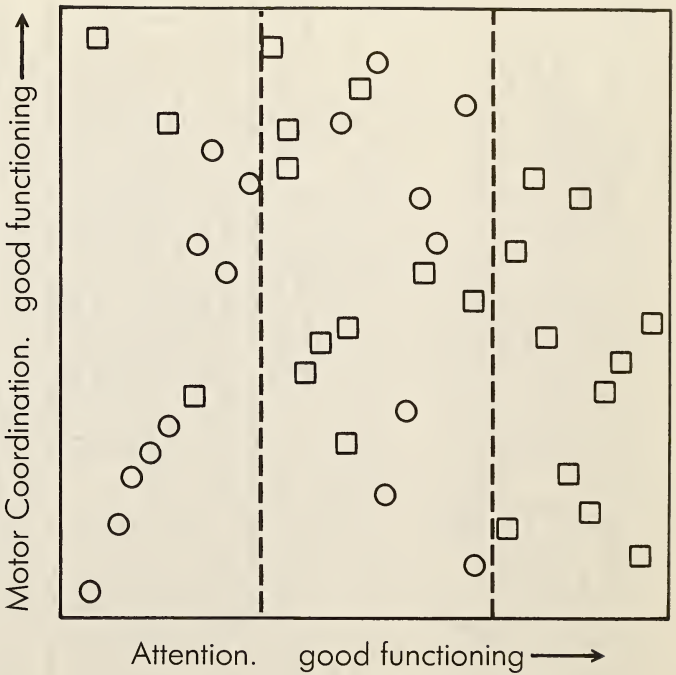

FIGURE 2. POSAC of 12-Month IBR Items.

○ = Methadone. □ = Comparison.

attentional variables were the better discriminators of the two groups. The infants functioning most poorly on the attentional variables (at the left of the figure) were predominantly from the methadone group (9 versus 3). The best functioning infants (at the right of the figure) were all from the comparison group (11 versus 0).

Figure 3 plots the joint directions of the 4- and 12-month POSAC's against each other. The abscissa represents 4-month motor and attentional functioning; the ordinate, 12-month functioning. There is a moderate degree of continuity in functioning across the two ages. For the control group the Pearson correlation between the two ages is +0.38; for the methadone group, near zero. The lack of an association between the two ages for the methadone group is due primarily to the performance of two individuals: one who showed a marked increase in performance across age and one who showed a marked decrease in performance across age. The figure indicates the regions of children who showed clinically poor functioning and good functioning at both ages. The ten consistently poor functioning infants included seven from the methadone group; the nine consistently well functioning infants included only two from the methadone group.

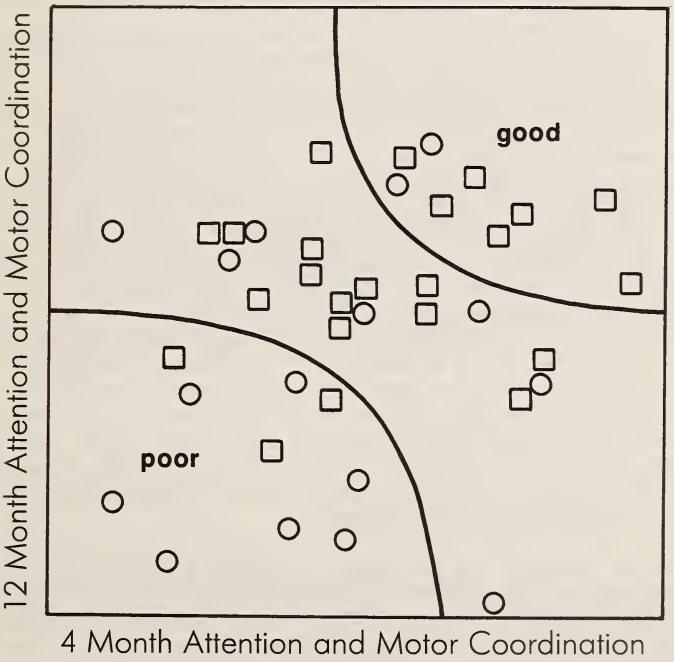

FIGURE 3. Scatterplot of 4- by 12-Month IBR Items.
○ = Methadone. □ = Comparison.

In order to be comparable to other at-risk studies in the drug field, a univariate repeated measures analysis of variance was computed using drug group as a between subjects factor and 4- and 12-month Mental Development Index (MDI) scores as repeated measures. There were no significant differences between groups, ages, or an interaction of the two. At four months, both groups had mean MDI scores of between 110 and 115; at twelve months, both had scores of 108. A similar analysis of Psychomotor Development Index (PDI) scores also revealed no significant differences for group or age by group. There was, however, a significant age effect with both methadone and comparison groups showing a decline in PDI from 4- to 12-months, dropping for both groups from means of approximately 117, to 107. Similar repeated measures ANOVA's were computed on the 8 IBR items representing attention, motor coordination, and activity level. On all items there was a statistically significant effect for age with 12-month-olds showing higher mean levels of attention, motor coordination, and activity. On two of the items there were group by age effects statistically significant at the .05 level, with 4-month-old methadone group infants having poor motor coordination and higher activity level than comparison group infants.

DISCUSSION

Poor attention, sometimes accompanied by poor motor coordination and hyperactivity, are characteristics of childhood attention deficit disorders. It is possible that these same behaviors in infancy represent the early stages of ADD. Our results indicate that a subgroup of infants exposed in utero to methadone showed deficits in both attention and motor coordination that often co-occurred. High activity level was also characteristic of some methadone group infants but did not co-occur with deficits in attention and motor coordination. The deficits in these areas show different patterns of emergence. Attention deficits in the methadone group infants emerge clearly at 12 months, while differences in motor coordination are disappearing at 12 months. It is possible that the motoric symptoms in some methadone-exposed infants at 4 months are merely indications of delayed or prolonged narcotic withdrawal, while the strong attentional deficits in a subgroup of methadone infants at 12 months are indicators of a new, more permanent neuro-behavioral syndrome. Further longitudinal follow-up is necessary to determine the stability of these attentional deficits into the toddler years. In addition, we are also investigating the effects of type of maternal drug use, infant perinatal problems, and parental neuropsychological functioning in determining infant behavior.

Measures of infant behavior do not generally show a high degree of continuity from one age to another. The relative stability in attentional and motor functioning across age in our comparison group infants serves to highlight the fluctuations in patterning of behavior in some of the methadone infants across this time period. One explanation for the lack of stability between 4 and 12 months in this group is the effect of narcotic withdrawal. Many of the symptoms of narcotic withdrawal in infants are similar to those behaviors used to assess central nervous system dysfunction. In the

methadone group infants at 4 months, the residual effects of narcotics in the system or symptoms of withdrawal may in some children mask their underlying level of CNS functioning.

In this sample, as in other reported research, there were no differences between drug-exposed and comparison infants on standardized tests of infant skill acquisition. There were, however, differences between the groups on scales that rated qualitative aspects of the infants' behavior made during the same time period. Standardized tests of ability are known to have poor predictive validity, and because they report global scores, they can offer no suggestions of the specific underlying physiological or anatomical deficits that may affect a group of children. Ratings of more qualitative aspects of behaviors, on the other hand, have already paid off in the field of behavioral teratology. During the neonatal period, drug-exposed infants differ in the quality of their motor behaviors (e.g., smoothness of movement, tenseness of limbs, strength of reflexes) rather than the presence or absence of behaviors in their repertoire. Likewise, we have now confirmed that post-natally such infants continue to differ in qualitative aspects of their motoric and cognitive functioning. We strongly advocate that future research with this population continue to explore such qualitative aspects of behavioral development.

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Complete reference will be supplied by the authors upon request.

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Predictors of Favorable Outcome Following Naltrexone Treatment

Robert A. Greenstein, Bradley D. Evans, A. Thomas McLellan, and Charles P. O'Brien

INTRODUCTION

Naltrexone is an opiate antagonist which has been used in the treatment of opiate addiction at our clinic during the past eight years. Naltrexone is an effective opiate blocker and appears to produce few unwanted side effects (Resnick et al. 1973). In addition several studies have indicated that patients show significant reductions in both opiate and non-opiate drug use and appear to improve in social and work adjustments (O'Brien et al. 1975; O'Brien and Greenstein 1976) during naltrexone treatment.

However, despite the safety and apparent effectiveness of naltrexone, the drug has not been well accepted by the patient population and therefore has not enjoyed wide use. Early investigators noted from the start that drop-out was high and that the average length of treatment was less than 30 days. For example, Hass et al. (op. cit.) and Hurzeler et al. (op. cit.) observed that more than half of their naltrexone patients returned to methadone maintenance after less than two months.

Several workers in the field have suggested potential reasons for the unpopularity of naltrexone and have attempted to promote better patient acceptance through lengthening the detoxification period (Greenstein et al. op. cit.), offering monetary incentives (Grabowski et al. 1979), providing extensive patient education (Goldstein op. cit.) and even combining it with psychotherapy. While all of these suggestions show promise, prior results suggest that it is unlikely that any of these interventions alone will increase the general acceptance of the drug significantly.

In the present paper, we have attempted to apply a different strategy to the naltrexone effectiveness question. We have completed a series of predictive analyses utilizing multivariate statistical procedures to define and describe the type of patient for whom naltrexone has had the most significant impact. Results of these analyses may make it possible to direct and promote naltrexone treatment to those patients who are potentially best suited for it.

STAGE I - PREDICTION OF ONE-MONTH OUTCOME

Previous work with naltrexone in our population (O'Brien et al. 1975; O'Brien and Greenstein 1976) showed that significant improvements in opiate and nonopiate drug use, employment, and several subjective ratings of physical and emotional status were seen at one month postnaltrexone followup. Thus, as a first step in identifying the patients most likely to benefit from naltrexone we used a range of patient demographic and pretreatment status measures as well as during-treatment performance measures in a multivariate regression analysis to predict patient status at one month following treatment.

METHOD

Subjects - Subjects were 89 naltrexone patients who completed induction (greater than six days) during their first treatment episode; sixty-nine (73 percent) of these subjects were interviewed one month following naltrexone termination by an independent technician. Urine samples for subsequent urinalysis were collected at the followup interview and "drug-free" status was strictly defined as subjective denial of drug use and confirmation by a negative urinalysis.

Procedure - A complete range of predictor variables were included in the BMDP step-wise regression analysis and these were divided into three categories. Demographic items included age, race, years of education, years of technical training, and number of prior drug abuse treatments. Pretreatment status measures included years of opiate and nonopiate drug use, hours worked, criminal activity and earnings in the month prior to naltrexone induction, lifetime arrests, months spent in prison, and self-reported ratings of family problems, health, leisure activity, anxiety, depression and thought confusion. During-treatment variables included days of naltrexone treatment, type of termination and a self-rating of satisfaction with naltrexone.

Four variables were used as outcome measures in the regression analyses and were measured for the month prior to the followup interview. Days of opiate use, days of nonopiate use, employment earnings, and self-reported criminal activity were each used as dependent variables. In each of these analyses, the predictor variables were sequentially entered into a regression equation and the procedure indicated the extent to which each of these variables was related to the outcome (dependent) measure. Only variables which were significantly ($p < .01$) related to outcome were selected by the regression equation.

RESULTS

The results of all regression analyses were essentially the

same. Only two predictor variables were significantly related to any of the outcome measures at the $p < .01$ level. Pretreatment employment earnings was significantly and positively related to better one-month outcome status on two measures (opiate use, posttreatment earnings), and this measure accounted for an average of 17 percent of variance across these two outcome measures. However, days of naltrexone treatment was significantly and positively related to better one-month outcome status, on all four outcome measures and explained an average of 30 percent of the outcome variance across these measures.

STAGE II - OPTIMUM LENGTH OF TREATMENT

The Stage I analyses indicated that the duration of naltrexone treatment (in days) was the best general predictor of one month posttreatment outcome. Thus, it became important to determine whether there was a minimum period of naltrexone treatment, below which posttreatment outcome was clearly poor.

METHOD

Subjects - Subjects were the same 69 naltrexone patients used in the
Stage I analysis.

Procedure - The patient sample was divided into subgroups based upon their treatment duration; less than 11 days, 11-20 days, 21-30 days, 31-50 days, 51-70 days, 71-100 days and greater than 100 days. Then, the relationship between naltrexone treatment duration and outcome was examined by charting the mean scores for each of our one-month followup criteria for each subgroup.

RESULTS

The results for two (Opiate Use, Earnings) of the four charts are presented in figures 1-2. The results are quite similar for all four criteria and two points were evident. First, patients who remained on naltrexone less than ten days had clearly worse outcomes. Opiate and nonopiate drug use was greater, and employment earnings were lower for those patients who completed 10 days or less of naltrexone treatment following induction.

A second aspect of the relationship between days of naltrexone treatment and one-month followup status is seen in the asymptotic nature of the charts at approximately one month (postinduction) of treatment. From one to approximately 30 days there is a clear and direct relationship between treatment duration and posttreatment status. That is, patients who stayed in treatment longer had better one-month posttreatment criterion scores on all four measures. However, at

approximately 30 days of naltrexone treatment the relationship becomes less pronounced and the performance equalizes, suggesting that post-treatment outcomes are not significantly better following treatments greater than one month. This aspect of the relationship was seen on all charts at approximately the same treatment duration point. It must be stressed that relatively fewer data points are available at treatment durations beyond 30 days and that patients who remained in treatment longer derived more prolonged benefit while they were on naltrexone, even though their followup results may be similar to those who stopped treatment at the end of the first month.

STAGE III - PREDICTION OF LENGTH IN TREATMENT

Although the duration of naltrexone treatment was positively related to one-month outcome as shown in Stages I and II, this measure was obviously of little value in predicting whether new patients would do well on naltrexone. However, we reasoned that if this variable were the best predictor of posttreatment outcome, then it might be possible to perform a second analysis to determine the patient variables which predicted longer durations of naltrexone treatment.

METHOD

Subjects - Subjects were 139 naltrexone patients who had completed induction on their first naltrexone treatment. This sample included all subjects from the Stage I study plus the remaining patients who had completed induction but had not been scheduled for followup.

Procedure - The same demographic and pretreatment status variables which were used as predictors in the Stage I analysis were again used in a multiple regression analysis, with days of naltrexone treatment as the outcome measure.

RESULTS

The multiple regression analysis indicated that two patient variables were significantly associated with length of naltrexone treatment at the $p < .01$ level. The marital status variable explained 17 percent of the variation. Patients who were married had significantly longer treatment durations than patients who were not married. Employment during the month preceeding naltrexone treatment was also significantly related to treatment duration and explained 11 percent of outcome variance. Together, these two predictor variables explained 26 percent of the variability in the duration of naltrexone treatment.

In an attempt to determine the type of patient most likely to benefit from opiate antagonist therapy, we performed a series of multivariate regression analyses on a sample of male veterans who completed induction on the opiate antagonist naltrexone during their drug abuse treatment. A range of patient background characteristics, demographic factors and during-treatment variables were used to predict outcome on four criteria measured at followup, one month after termination of naltrexone therapy. Only two measures – employment at the start of naltrexone and length of naltrexone therapy – were significantly related to better outcome at one-month follow-up. Of these, treatment duration was clearly the best outcome predictor. The finding that at least thirty days of naltrexone therapy was necessary for significant improvement at one-month followup but that longer periods of treatment were not necessarily associated with greater gains suggests that treatment can be limited and still be relatively successful. Perhaps a minimum period of treatment is necessary to overcome the conditioning factors that can lead to readdiction. In fact, much of the rationale for antagonist therapy is based on the premise that drug-taking behavior can be extinguished by eliminating the reinforcement produced by opiates. The necessity for a minimal treatment duration can also be consistent with a purely biological explanation. For example, chronic opiate dependence may significantly affect central nervous system neurophysiology, and some minimal period or "recovery time" may be necessary to return to the preaddiction physiological state.

In a second set of analyses in which we attempted to discover patient characteristics predictive of longer treatment duration, it was shown that patients who were employed and/or married at the start of naltrexone therapy were more likely to stay in treatment longer. Similar results were obtained by others. Lewis et al. (1978) for example, showed that 66 percent of his patients who stayed on naltrexone more than two months were married as compared with only 13 percent of those who left treatment prior to the two-month point. Resnick et al. (op. cit.) also found that employed patients spend more time on naltrexone, and were more likely to be opiate free at one year follow-up. Further, studies by Myers et al. (1975) showed that chronically unemployed patients were most likely to drop out of inpatient naltrexone therapy prior to the recommended one to two months of therapy. One obvious direct explanation for these results would be that these patients have the best family and social supports to sustain a positive treatment outcome. In addition, they may also be more "motivated" since they have the most to lose personally and financially by readdiction.

Another possible indirect explanation for these results relates

to our prior work attempting to predict outcome from therapeutic community and methadone maintenance treatments (McLellan et al. in press). In these studies we found that a global estimate of the seriousness of a patient's psychiatric symptomatology-- their "psychiatric severity"-- was the best general predictor of outcome. A suitable measure of overall "psychiatric severity" was not available in the present patient sample, but there is suggestive clinical evidence that this factor may also be important in predicting treatment outcome for naltrexone therapy. For example, we have observed that some patients who drop out of treatment early do so because of excessive anxiety and dysphoria during the induction period. Others have made similar observations. Lewis et al. (1978) observed that patients who stayed in treatment less than eight weeks were more depressed and angry at baseline in addition to being more anxious and tense at three weeks than those who stayed in treatment longer than eight weeks. Considering the present results in this light, it may be that those patients who were working and/or married were more psychologically "stable" than their unemployed, single counter parts, and better able to tolerate the stresses of drug-free living. It might be useful for a future study of naltrexone treatment to determine whether or not psychiatric severity predicts posttreatment outcome and if so, what effect adequate psychotropic medication for anxiety and depression would have on retention and outcome. Historically, our psychiatrically heterogeneous population was treated "drug free" with naltrexone only; and a patient simply made it or not pretty much on his own. Theoretically, the extended use of appropriate anxiolytic and antidepressant medications during the induction period and during the critical first month of treatment should help the most dysphoric patients stay in treatment longer and therefore have a better chance for a positive outcome. We are presently reviewing 26 consecutive naltrexone patients, some of whom were prescribed additional psychotropic medications during their naltrexone induction and maintenance treatment. The results from these and additional patients treated in this manner will be the subject of a future report.

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Due to space limitations, references are available from the senior author upon request.

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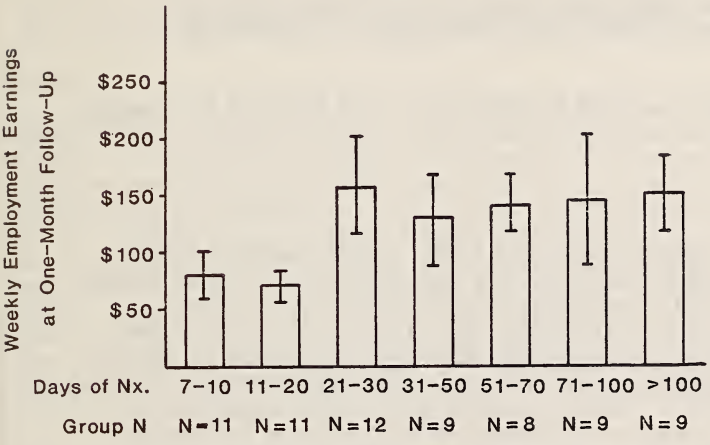
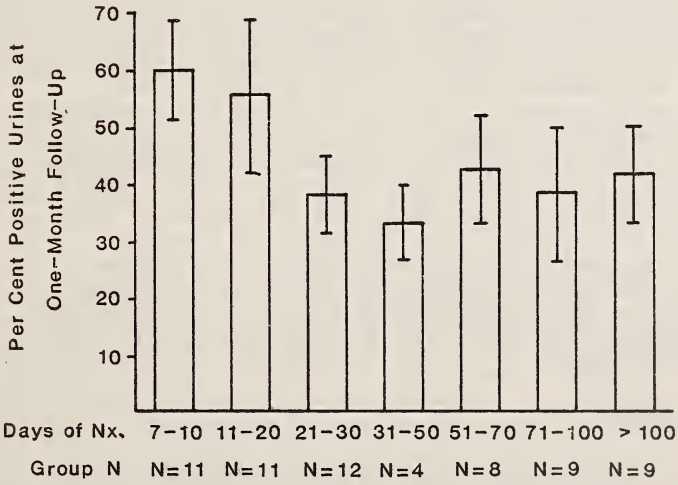
Earnings at One-Month Follow-Up By Duration of Naltrexone Treatment



Opiate Used at One-Month Follow-Up By Duration of Naltrexone Treatment



Addressing the Diversion of Take-Home Methadone: LAAM as the Sole Treatment Choice for Patients Seeking Maintenance Therapy

Gordon Hough, Arnold M. Washton, and Richard B. Resnick

INTRODUCTION

In a series of papers published between 1969 and 1972, Jaffe et al.(1969, 1970a, 1970b, 1972), showed that supervised administration of LAAM three times a week in the clinic allows maintenance of the opioid-dependent patient without take-home doses. Subsequent studies have established a record of safety for LAAM maintenance (Ling, et al., 1976, 1978, Blaine, et al., 1976, 1978, 1981). During the last ten years, moreover, widespread diversion of take-home methadone doses has become a public health problem of major concern (Goldstein and Judson, 1974).

An approach to curtailing methadone diversion might include restricting or eliminating take-home methadone and offering LAAM as the only alternative for patients who desire reduced clinic visits, an approach offered first by Goldstein (1976). In 1981 we reported a clinical trial which tested the feasibility of conducting a maintenance program where patients chose either LAAM, requiring three clinic visits per week, or daily methadone requiring six clinic visits per week. (Resnick, et al., 1981.) That study indicated that such a choice was acceptable as long as patients were not eligible under FDA rules for take-home methadone. It appeared to us that availability of methadone at all complicated evaluation of LAAM's acceptability. We began a protocol in which only LAAM was offered to maintenance patients in hope of providing a clearer trial of LAAM's acceptability as a maintenance treatment.

PATIENTS AND METHODS

During an 11-month period from the beginning of February through December, 1981, patients requesting methadone maintenance treatment were told on their first contact before an appointment was set for an intake interview that we offered maintenance using LAAM only. Potentially eligible patients included those

enrolled in methadone maintenance treatment and persons addicted to illicit opiates.

Patients who elected to enter LAAM maintenance had to meet the following requirements for acceptance onto the program: FDA and New York State requirements for methadone maintenance; absence of serious medical or psychiatric illness; no abuse of non-opiate drugs or alcohol. In addition, women of child-bearing potential could not be pregnant. During the first three weeks on LAAM, patients could come to the clinic on alternate (non-LAAM) days for a supplemental dose of methadone (usually 10-15 mgs).

RESULTS

Seventy-four patients entered LAAM treatment during the 11-month period. Twenty-six switched to LAAM from methadone maintenance treatment and 48 entered LAAM from addiction to illicit opiates (heroin and/or methadone). Forty-eight patients were males and 16 were females. At the end of the 11-month period (as of January 31, 1982), 72% of the patients who entered LAAM maintenance were still in treatment and 28% had discontinued LAAM. Table 1 lists the reported reasons for discontinuing LAAM for the 21 subjects who terminated LAAM treatment during the study period. As can be seen, 15 patients terminated for reasons unrelated to LAAM itself and only 6 terminated because of reported dissatisfaction with LAAM.

The most common LAAM-related complaint concerned problems experienced during the 72-hour weekend period beginning with the Friday dose. Patients complained that the Friday LAAM dose, which was usually at least 10 mgs higher than the Monday and Wednesday dose, resulted in their feeling over-medicated on Friday and feeling under-medicated on Sunday.

It is of interest to note that patients who discontinued LAAM treatment tended to do so early in treatment. Among those who discontinued LAAM the average retention in treatment was 7.6 weeks (range 1 to 26 weeks) as compared to an average of 27 weeks (range 4 to 52 weeks) for patients who continued on LAAM.

Table 2 presents LAAM retention data for the methadone maintenance patients as compared to the illicit opiate users. Table 3 presents the data for male vs. female patients. As shown in the tables, retention in LAAM treatment did not differ significantly between methadone patients and illicit opiate users, nor did it differ significantly between males and females. No reaction to LAAM was peculiar or distinctive to females as opposed to males.

Additional information was obtained on the acceptability of LAAM when our clinic was closed for two consecutive days on holidays. Patients could choose to remain on LAAM and change their medication days, or to switch to methadone, e.g., because of travel plans. Each alternative produced no complaints, with one exception: patients not yet stabilized on LAAM experienced withdrawal symptoms when switched to methadone and again when

returned to LAAM.

DISCUSSION

This study suggests that LAAM is a clinically viable treatment drug in a setting where take-home methadone is available in nearby clinics to patients who meet necessary eligibility requirements. Six other clinics are within twelve blocks of ours. Patients continued to enroll in our program and remained in treatment past the time when they could have applied to transfer to another clinic after they became eligible for take-home methadone. Acceptance and retention in treatment were regarded as satisfactory.

The majority of drug-related drop-outs - four of six - were patients who felt over-medicated on Friday and under-medicated the Sunday following. Probably a reduction in LAAM dose and an increase in supplement would address this problem. However, it should be noted that one of the four drop-outs for this reason had had a previous treatment episode on methadone in our clinic. She was a demanding patient with very low frustration tolerance: we have some reason to doubt whether she was ready or able to deal with every other day medication, because, among other things, she had received considerable attention from the staff on virtually every clinic visit when maintained on methadone. Our experience in the past has suggested that patients with poor psychosocial functioning may have difficulty with LAAM treatment (Resnick, et al., 1976).

In this study we were motivated by concern about methadone diversion and wished to explore the feasibility of discontinuing take-home methadone without penalizing working patients by requiring daily clinic visits. Methadone diversion is rife in the East Harlem neighborhood of our clinic. Should the FDA act favorably on an NDA for LAAM, this drug should offer a viable, non-punitive alternative to daily clinic visits in communities where methadone diversion is a hazard to public health.

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TABLE 1

REASONS FOR DISCONTINUING LAAM MAINTENANCE

(N = 21)

		# SUBJECTS
I.	RELATED TO LAAM (N = 6)	
	a. Felt overmedicated Friday and undermedicated Sunday	4
	b. Insomnia & bad dreams	2
II.	UNRELATED TO LAAM (N = 15)	
	a. Pregnancy	1
	b. Administrative detox due to non-payment of fees	2
	c. Hospitalization unrelated to LAAM	1
	d. Voluntary detoxification	7
	e. Miscellaneous others	4

TABLE 2

RETENTION IN LAAM TREATMENT FOR METHADONE MAINTENANCE PATIENTS VS. ILLICIT OPIATE USERS

		METHADONE MAINTENANCE PATIENTS	ILLICIT OPIATE USERS	TOTAL
SUBJECTS STARTING LAAM	N	26	48	74
	(%)	(100%)	(100%)	(100%)
SUBJECTS STILL ON LAAM AS OF 1/31/82	N	17	36	53
	(%)	(65%)	(75%)	(72%)
SUBJECTS WHO DISCONTINUED LAAM	N	9	12	21
	(%)	(35%)	(25%)	(28%)

TABLE 3

ACCEPTABILITY OF LAAM IN MALES VS. FEMALES

		MALES	FEMALES	TOTAL
SUBJECTS STARTING LAAM	N	58	16	74
	(%)	(100%)	(100%)	(100%)
STILL ON LAAM	N	42	11	53
	(%)	(72%)	(69%)	(72%)
DISCONTINUED ON LAAM	N	16	5	21
	(%)	(28%)	(31%)	(28%)

Efficacy of Psychotherapeutic Counselling During 21-Day Ambulatory Heroin Detoxification

R. A. Rawson, A. J. Mann, F. S. Tennant, Jr., and D. Clabough

ABSTRACT

Structured, psychotherapeutic counselling during 21-day heroin detoxification was evaluated by randomly assigning a group of 25 heroin addicts to a detoxification treatment regimen with mandatory counselling by a therapist and 25 to a control group who received only standard detoxification without counselling. There was no significant difference between groups in the number who successfully detoxified as measured by conversion of morphine positive urine to morphine negative urine. The counselling intervention group did, however, improve the attendance of subjects while in detoxification treatment, and significantly more patients entered long-term treatment following detoxification. Maximal use of a counselor during 21-day heroin detoxification may best be realized by directing therapy toward engaging patients in long-term care.

INTRODUCTION

The contribution of psychotherapeutic counselling in combination with pharmacotherapy for the treatment of heroin addiction has received little critical evaluation. (Kuncel, 1981; Brown, Jackson, and Bass, 1973; Ramer, Zaslone, and Langan, 1971) Experienced clinicians suggest that counselling is a necessary adjunct to methadone treatment, but little data exists to justify the expense incurred by the use of counselling during medical detoxification. In addition, if counselling is useful as an adjunct to detoxification, the specific aims and goals of the counselling intervention need to be clearly defined. The purpose of this study was to evaluate the efficacy of psychotherapeutic counselling as an adjunct to the widely used 21-day ambulatory methadone detoxification program.

METHODS

Fifty (50) heroin-dependent patients seeking admission to a 21-day methadone detoxification program served as subjects. There were 33 male and 17 female subjects, who ranged in age from 18 to 54 years ($\bar{X}$ = 30.0 years). Subjects reported mean heroin

dependency of 8.8 years and had previously attempted detoxification a mean of 4.0 times. No significant difference between treatment groups was demonstrated on any demographic or drug-use variable.

Subjects were assigned according to a random numbers table to one of two treatment groups; a group receiving detoxification with counselling (C), or no counselling (NC). Detoxification was ambulatory and the dosage began at 35 mg on the first day and decreased systematically to zero over 21 days. This technique is standard in the United States. (6) The NC group was allowed to progress normally through the standard 21-day detoxification regimen with no attempts made to engage patients in a counselling relationship. These subjects were provided with referrals for counselling to local agencies and given information on long-term treatment modalities by the dispensing nurse only when the patient inquired about them. Subjects in the C group were required to participate in a mandatory counselling session on the second dosing day. Subsequent non-mandatory sessions were scheduled during the second and third weeks of treatment. Counselling sessions averaged approximately 15 to 20 minutes in length. Sessions followed a format similar to that proposed by Wolberg (7) and utilized by Woody (8) in their investigations of the efficacy of psychotherapy techniques in methadone treatment. This form of drug counselling entails the assessment of individual patient's needs and the provision of services to meet these needs. Discussion of the problems surrounding relapse and the availability of long-term treatment to addicts was included. Treatment options that were available and which the patient was educated about included methadone, naltrexone, and propoxyphene napsylate maintenance; drug-free psychotherapy; and residential therapy. No attempt was made to mediate intrapsychic processes or engage in any specific form of psychotherapeutic techniques. All counselling sessions were conducted by one counselor with a master's degree of psychology who was experienced in drug abuse treatment.

A urine specimen was collected at admission and during each subsequent week. It was analyzed for morphine in order to determine if heroin abuse ceased during detoxification. Futher evaluation was done by determining drop-outs during the 21-day program and the number who entered long-term treatment following 21-day detoxification. Long-term effects of counselling were assessed by contacting all subjects and doing oral interviews with subjects six months after detoxification was completed.

RESULTS

Table I presents a comparison of outcome in the two groups. Counselling intervention had no impact on the number of subjects who completed the full 21-day detoxification program, or the number who converted urine from morphine-positive on admission to morphine-negative. The C group had significantly fewer drop-outs and an increased rate of transfer to a long-term treatment

modality. In addition, the C group had increased compliance in attending scheduled medication visits during the detoxification treatment.

Another indication that counselling intervention increased retention in treatment is that, of those subjects who attended one or more of the non-mandatory counselling sessions, 82% (9 of 11) continued in long-term treatment, while only 43% (6 of 14) of those who did not attend a non-mandatory counselling session retained in long-term treatment ($X^2 = 3.8$; $P < .05$). Although it was impossible to contact 19 of 50 subjects at six months follow-up, there was the suggestion that counselling intervention may have resulted in retaining more subjects in long-term treatment. (Table II)

DISCUSSION

The results of this study suggest that counselling may have a significant impact on the efficacy of the 21-day methadone detoxification program which is widely used in the United States. (6) Data in this study shows that counselling during ambulatory 21-day methadone detoxification primarily results in a higher rate of patient transfer to long-term treatment.

Several studies indicate that a heroin addict best benefits from long-term treatment. (6,9,10) Simpson (9) surveyed major drug treatment modalities and found that on virtually all psychosocial, medical and drug use indices, an addict in treatment is benefited more than an addict out of treatment. Others have demonstrated that addicts in treatment are much more productive to society and require less social cost than those not in the treatment. (1,10)

Although various investigators have argued for the addition of counselling to methadone treatment, there has been little data to support this belief. (3) Data from this study suggests that a counselor should best direct intervention toward the goal of engaging the patient in long-term treatment rather than short-term benefits. To implement such a strategy, the counselor must be skilled in developing rapport, have knowledge of long-term treatment, and have available the necessary treatments to provide long-term treatment.

TABLE I

OUTCOME OF TWO DETOXIFICATION TREATMENTS

	Counselling Group N=25	No Counselling Group N=25	Statistical Significance
Completion of a 21-day program.	4 (16%)	3 (12%)	NS
Subjects with a morphine-negative urine sample during treatment.	15 (61%)	13 (53%)	NS
Mean days in detoxification treatment.	14.0	12.8	NS
Subjects who dropped out of treatment	9 (36%)	17 (68%)	$P < .025$
Subjects who transferred to long-term treatment	12 (48%)	4 (20%)	$P < .05$
Scheduled medication visits attended while on detoxification program	377/460 (82%)	313/482 (65%)	$P < .01$

TABLE II

SIX-MONTH FOLLOW-UP STATUS

	Counselling Group N=25	No Counselling Group N=25	Statistical Significance
In continued treatment for six months.	8 (32%)	4 (16%)	NS
Re-addicted to illicit drugs or incarcerated.	7 (28%)	12 (48%)	NS
Unable to contact at six months.	10 (40%)	9 (36%)	NS

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Outpatient Treatment of Prescription Opioid Dependence: Comparison of Two Methods

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ABSTRACT

Outpatient treatment of 42 patients who presented with dependence upon prescription opioids was attempted by two different methods. The first group of 21 patients was treated by 21-day detoxification followed by psychotherapeutic counseling (D/C), and the next 21 patients were offered 21-day detoxification to be followed by opioid maintenance if detoxification was unsuccessful (D/M). Only 5 of 21 (23.8%) patients in the D/C group compared to 20 of 21 (95.2%) in the D/M group completed three weeks of treatment ($P < .001$). On admission, no patient perceived that chronic pain due to a medical condition would be an impediment to withdrawal from opioids, but pain which was masked by opioid dependency and which emerged during detoxification proved to be an insurmountable barrier to total withdrawal in the majority of patients. Treatment of outpatients who presented with dependence upon prescription opioids was best provided in the study by opioid maintenance and adjunctive pain therapy.

INTRODUCTION

Although there is voluminous data on the treatment of heroin dependence, treatment of outpatients who present with dependence on prescription opioids has not been systematically studied. (1,2) Reported here is a series of 42 consecutive patients who voluntarily sought outpatient withdrawal from prescription opioid dependence. Patients were treated by one of two methods. The first 21 patients were treated by a three-week detoxification schedule with post-withdrawal psychotherapy, and the second 21 patients were offered three-week detoxification to be followed by opioid maintenance if withdrawal was not successful. The primary opioid of dependence, precipitating cause of opioid use, medical regimens used in the treatment, and outcome of treatment are described.

METHODS

Forty-two (42) patients volunteered for outpatient treatment between January, 1979 and September, 1981. All patients obtained opioids from one or more physicians. On admission, patients

completed a written medical and drug history, received a complete physical examination and submitted a urine for drug analysis. The daily dosage of opioid and reason the patient began taking the drug was determined. The first 21 patients in the study entered a three-week detoxfication program which administered standard doses of methadone, propoxyphene napsylate, clonidine, or symtomatic relief with diphenoxylate and sedative-hypnotics. (3-6) Patients attended the clinic each day. Detoxification was to be followed by weekly psychotherapeutic counseling with a psychologist (D/C). The next 21 patients admitted to the study entered one of the above detoxification regimens, and they were informed on day one of treatment that they could be maintained with an opioid if detoxification was unsuccessful (D/M) as judged by the patient's inability to refrain from opioid use.

Maintenance regimens offered were methadone or propoxyphene napsylate unless the patient was found to have significant cause of chronic pain which would qualify the patient to receive other opioids and be registered as a medical addict with the California Attorney General. (6-8)

Patients who chose maintenance attended the clinic for psychotherapy and medical treatments two times per week for the first month; weekly the second month, and bi-monthly thereafter. The initial maintenance dose was gradually reduced over time as any associated painful condition was successfully treated. The treatment team consisted of a physician, nurse practitioner, and two psychologists. Psychotherapeutic counseling sessions lasted approximately 30 minutes and often included family members. Pain treatments included anti-depressants, physical therapy, non-opioid analgesics, localized steroid injections, and electrical stimulation. (9) Naltrexone was available for patients who could gradually withdraw and achieve a drug-free state. (10)

RESULTS

Table One shows demographic and drug-use data for both study groups. The statistically significant difference between groups was in mean age. The majority of patients began their prescription opioid dependence due to a painful medical problem (Table Two). Accident or injury, headaches, post-surgical pain, or back or spine disorder were the major initiating causes of opioid use. Nine (9;21.4%) patients could not give a reason for beginning opioid use. Although a total of 13 of 21 (61.9%) in the D/C group, and 15 of 21 (71.4%) in the D/M group claimed to have chronic, persistent pain at the time of admission, no patient in either group initially perceived that their pain was severe enough to interfere with total withdrawal from opioids. This belief proved false since significant pain emerged during the detoxification phase in the majority of patients. The most common opioids of dependence were codeine, propoxyphene, and oxycodone (Table Three). Codeine accounted for 24 of 42 (57.1%) subjects. Mean daily dosage ranges were compatible with a significant degree of physical dependence. (8) Table Four shows the

detoxification agent attempted in both groups. Twenty of 21 (95.2%) subjects in the D/M group requested maintenance at some point during detoxification. Following are the opioids used for maintenance, the number of patients administered each drug, and the approximate average daily dosage used for maintenance: propoxyphene napsylate (9; 1200 mg); codeine (5; 700 mg); hydromorphone (3; 40 mg); oxycodone (2; 55 mg); and levorphanol (1; 20 mg). All the patients maintained with opioids other than propoxyphene napsylate were found to have such pain secondary to medical problems that they qualified to be a legally registered medical addict. (8)

Only 5 of 21 (23.8%) patients in the D/C group compared to 20 of 21 (95.2%) patients in the D/M group retained in treatment past three weeks ($P < .001$) (Table Five). After 90 days past admission, two patients in each group were opioid abstinent at this time point as judged by history, a urine test negative for morphine and other opiates, and no further requests for opioid prescriptions. Two additional D/M patients achieved abstinence within 180 days by gradually reducing the daily maintenance dose. One of those patients entered naltrexone maintenance in order to remain abstinent. Sixteen (16; D/M) patients remained in maintenance treatment for periods ranging from 3 to 18 months (mean, 12 months). After 15 months, one codeine-dependent patient was able to totally cease codeine use and maintain on the non-steroidal, non-opioid, benoxaprofen.

DISCUSSION

Patients in this study exhibited several common characteristics. The majority began opioid dependence following the occurrence of accident or injury, surgery, headaches, back, or spine disorder, or arthritis. None appeared to develop dependence accidentally, but developed dependence by taking opioids over a considerable period of time, (11) Most common opioids of dependence were codeine, propoxyphene, and oxycodone. In contrast to patients who obtain opioids, such as heroin, on the illegal market, these patients were predominantly white, older, middle-class, and 50% were female. (1) The difference in outcome between D/C and D/M groups appears significant. Since 16 of 21 (76.2%) patients in the D/C group, compared to 1 of 21 (4.8%) in the D/M group, dropped out of treatment during the first three weeks, it appears that retention is best achieved by assuring the patient that opioid maintenance will be provided for at least a temporary period. This finding supports those of Senay and Showalter who have recently shown that 84-day detoxification from methadone produces far better results than 21-day detoxification.

It is possible that outcome with these patients could have been improved if the patients had been hospitalized, although published studies comparing inpatient and outpatient outcomes of drug-dependent persons do not show any advantage of one treatment over the other. (13,14) Recently, inpatient opioid detoxification with clonidine and inpatient pain treatment have been highly

touted, so it is possible that inpatient treatment could have produced better long-term outcomes than observed in this study, (15-16) Clonidine was used to detoxify 7 patients in this study, but it did not produce results superior to other detoxification agents. At this time, there is no evidence to indicate that persons dependent on prescription opiods could be better treated on an inpatient basis, and until such evidence is available, the extra cost of inpatient treatment should be a factor in selection of treatment site.

Outcome in the D/C group was similar to that found with outpatient heroin detoxification. (17) The inability to withdraw patients in this study provides additional data to considerable animal and human evidence that opioid dependence may be a chronic intractable problem that may last years, and possibly a lifetime. (18-19) Opiates should, therefore, only be prescribed as a last resort in patients with chronic pain. (21) The role of chronic pain secondary to a medical condition in these patients proved to be very important. Even though 28 of 42 (66.5%) stated at admission they had chronic, persistent pain, none initially believed it to be an impediment to complete withdrawal from opioids. As withdrawal began, however, the majority of patients began to experience unmasking of significant pain which probably caused many patients in the D/C group to drop out of treatment, and the majority in the D/M group to request opioid maintenance. It was necessary to provide adjunctive pain treatment as well as opioid maintenance to retain patients in treatment.

Retention of the D/M group in long-term treatment appeared to be related to informing the patient that opioid maintenance would be available if 21-day detoxification was unsuccessful. Even though this assurance may make some patients less motivated to totally withdraw from opioids, the extremely high drop-out rate in the D/C group does not support a simple withdrawal and counseling technique. Long-term treatment has been shown to be more effective than short-term treatment for several types of drug problems. (12,22) Outpatient opioid maintenance with adjunctive pain treatment produced more opioid-abstinent patients, although not a statistically significant number, at the end of 180 days.

TABLE ONE

CHARACTERISTICS OF 42 PATIENTS DEPENDENT ON PRESCRIPTION OPIOIDS

	Detox/ Counseling N=21	Detox/ Maintenance N=21
Age Range (years)	21 - 67	26 - 73
Mean Age	33.4	44.1
Male (no. of patients)	11 (52.4%)	10 (47.6%)
Female (no. of patients)	10 (47.6%)	11 (52.4%)

Employed (no. of patients)	9 (42.9%)	8 (38.1%)
Length of Narcotic Use (range in years)	3 - 16	2 - 34
Mean Length Opioid Use	7.2 yrs.	9.2 yrs.
White	17 (80.9%)	18 (85.7%)
Hispanic	2 (9.5%)	2 (9.5%)
Black	2 (9.5%)	1 (4.8%)

+ Is statistically significant at the $P < .05$ level

TABLE TWO

REASONS FOR INITIATION
OF PRESCRIPTION OPIOID USE

	Detox/ Counseling N=21	Detox/ Maintenance N=21
Accident or Injury	2 (9.5%)	1 (4.8%)
Headaches	3 (14.3%)	5 (23.8%)
Post-Surgery	4 (19.0%)	5 (23.8%)
Back/Spine Disorder	5 (23.8%)	4 (19.0%)
Arthritis	2 (9.5%)	0
Unknown	5 (23.8%)	4 (19.0%)
Trigeminal Neuralgia	0	2 (9.5%)

TABLE THREE

PRIMARY OPIOIDS OF DEPENDENCE

	Range of Daily Dose (MG)	Approx. Mean Daily Dose (MG)	No. in Detox/ Counseling N=21	No. in Detox/ Maintenance N=21
Codeine	240 - 2400	800	14 (66.7%)	10 (47.6%)
Propoxyphene	975 - 1950	1400	2 (9.5%)	5 (23.8%)
Oxycodone	30 - 60	40	3 (14.3%)	2 (9.5%)
Hydromorphone	48 - 72	65	1 (4.8%)	1 (4.8%)
Pentazocine	500 - 800	600	1 (4.8%)	1 (4.8%)
Morphine	75 - 105	90	0	1 (4.8%)
Meperidine	100 - 300	190	0	1 (4.8%)

TABLE FOUR

DETOXIFICATION AGENT USED TO DETOXIFY
42 PRESCRIPTION OPIOID ADDICTS

	Detox/ Counseling N=21	Detox/ Maintenance N=21
Propoxyphene Napsylate	11 (52.4%)	11 (52.4%)
Methadone	4 (19.0%)	5 (23.8%)
Clonidine	4 (19.0%)	3 (14.3%)
Symptomatic	2 (9.5%)	2 (9.5%)

TABLE FIVE

OUTCOME OF TREATMENT

	Detox/ Counseling N=21	Detox/ Maintenance N=21
Did not return for a second clinic visit+	5 (23.8%)	0
Dropped out in first 3 weeks of treatment+	11 (52.4%)	1 (4.8%)
In treatment 90 days after admission	NA	18 (85.7%)
Abstinent on the 90th day following admission	2 (9.5%)	2 (9.5%)
Completed detoxification, but relapsed within 90 days	3 (14.3%)	NA
Abstinent on the 180th day following admission	2 (9.5%)	4 (19.0%)

+ Is statistically significant at the $P < .05$ level

* One patient achieved opioid abstinence by use of naltrexone maintenance

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Prevalence and Implications of Multi-Drug Abuse in a Population of Methadone-Maintained Women

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The Family Center Program in Philadelphia is a multi-focal program encompassing medical and psychosocial services for drug-dependent pregnant women. On admission to our out-patient program, patients are stabilized on a methadone dose adequate to prevent withdrawal symptoms, with the average patient receiving a daily dose of 40 mg. It is not uncommon for our patients to need an increase in their methadone dose as their requirements for stabilization of withdrawal symptoms increase with the normal course of pregnancy. However, although requests for increases in methadone are rarely refused by our clinic physicians, we still see 74 percent of our patients using heroin. In addition, non-opiate drug abuse is a problem in our population. Knowledge of multi-drug abuse, as ascertained by urine toxicology reports, has a number of uses in addition to the legal requirements. Weekly urine toxicology reports are used by the Family Center staff as a clinical tool to measure treatment efficacy, to evaluate whether the patient is on an adequate dose of methadone, and as a possible indication that the patient may be self-medicating symptoms of anxiety or depression. Knowledge of the specific agents of abuse are also pertinent to the appropriate treatment of the infants prenatally exposed to drugs.

Many programs (Kornblith, 1981; Budd, 1979; Budd, 1980; Kokoski, et al. 1973; Senay, et al., 1977, Langrod, 1970; Kokoski, et al.; 1974) have reported on the frequency with which multi-drug abuse occurs among methadone maintained patients. However, the methodology does not always present an accurate representation of the extent of this problem. The extent of multi-drug use has often been calculated by the percent of urine samples positive for the specified agent (Kornblith, 1981; Budd, 1979; Budd, 1980; Kokoski, et al., 1973; Senay, et al., 1977). This methodology does not accurately reflect the prevalence of illicit drug use in the population under study. The urine samples are not independent measures since more than one sample per patient is obtained. Repeated measures are involved and mathematical analysis must be appropriate for this situation. Reporting on the proportion of patients ever using specified drugs - for program evaluation purposes - or the percent of urines per patient positive for specified drugs - for patient care - will result in a far more realistic measure of multi-drug use.

Methods

In order to determine the extent of multi-drug use among our patients, we studied a population of 100 women who had been admitted to the Family Center Program between 1978 and 1981, were maintained on methadone, and remained on the program long enough for us to have

obtained a minimum of 20 urine samples per woman (about four months). This population cannot be considered as a representative sample of methadone patients on all other programs because they are: female, pregnant, and stayed on the program for at least four months. The period of time during which the urine samples were collected included both the pregnant and postpartum states for each woman. The average number of urine samples collected per patient was about 40, for a total of 3,980 toxicology reports. Urine samples are collected by the medicating pharmacist at the initial clinic visit and/or hospitalization, once a week on a random schedule during the time the patient is on methadone maintenance, and at admission for delivery. In addition, any time a patient misses one or more consecutive doses of methadone, she is required to provide a urine sample before being medicated again. The urine samples are sent daily to our hospital laboratory where they are analyzed using the thin-layer chromatography technique which screens qualitatively for:

Laboratory Analysis, Thin-Layer Chromatography (TLC)

Methadone	Amphetamine	Dilantin
Phenobarbital	Methamphetamine	Demerol
Secobarbital	Morphine	Codeine
Other Barbiturates	Quinine	Phenypropanolamine
Doriden	Dilaudid	Pentazocine
Cocaine	Propoxyphene	Phencyclidine

In addition, the enzyme monitored immunoassay test is utilized to detect the presence of benzodiazepines, which, along with their metabolites are all reported as "diazepam" for which we also get a quantitative report. The range of values reported is 1) more than zero to 0.5 micrograms/ml, 2) more than 0.5 to 5 micrograms/ml, and 3) more than 5 micrograms/ml.

The variables studied include specific drugs of abuse, frequency of abuse and association of levels of abuse with methadone dose. The data was analyzed utilizing Pearsons Correlations, Analysis of Variance, Chi-square and Student-T tests of significance.

Results

In total, 98% of the study population were multi-drug users. There were three drugs of abuse which occurred with sufficient frequency to cause concern: heroin, diazepam and amphetamines. Correlational analysis did result in a highly significant ($p<.001$) degree of association between drugs within classes. Patients using one type of depressant were highly likely to be using another and not to be taking stimulants. Patients, when abusing drugs other than narcotics, tended to stay within specific drug classes. In Table I the frequency of use of heroin, diazepam and amphetamines is presented first as results of the urine toxicology reports from the population of 100 women calculated as percent of the total, i.e., percent of the 3,980 urines that were positive for the drug specified; secondly as results of calculating percent of the population of 100 Family Center patients who had one or more urines positive for the specified agent; and lastly as percent of population who had urines positive for the individual drugs 10% or more of the time, so as to eliminate those

who were occasional users. It is evident that use of drugs, when reported according to percent of patients ever using, shows a far graver picture. Although 28 percent of the urines were positive for heroin, 74 percent of the patients had a urine sample positive for heroin at least once and 58 percent had a positive report 10% or more of the time. Similar patterns are also found for diazepam and amphetamines.

Table I

How Calculated:	Pharmacologic Agents Detected in Addition to Methadone		
	Heroin	Diazepam	Amphetamines
Percent of urines positive for specified agent.	28%	45%	10%
Percent of women who had urines positive at least once.	74%	90%	67%
Percent of women who had urines positive 10% of the time.	58%	81%	31%

Analysis of the results with regard to level of use of heroin, diazepam and amphetamines is presented in Table II. The patterns of level of use differ between the drug categories. Those using diazepam tended to use it frequently, with 68 percent of the women having 20 percent or more of their urines positive for the drug. Those using amphetamines are more often occasional users, with only 18 percent of the patients having 20 percent or more of their urines positive for this drug. Patients using heroin are more evenly distributed across the level of use categories.

Table II

Percent of Urines Positive for specified drug (usage level)	Percent of women according to usage levels		
	Heroin	Diazepam	Amphetamines
None	26%	10%	33%
1 to 9%	17%	9%	16%
10 to 19%	14%	13%	13%
20 to 49%	16%	29%	15%
50-79%	20%	21%	2%
80%+	7%	18%	1%

Because methadone is a treatment for opiate-dependent persons, it would seem likely that there should be a relationship between methadone dose and heroin use. In Table III the percent of urines positive for heroin is presented according to category of daily methadone dose, i.e., those 19 patients who were receiving 30 to 35 mg/day of methadone had, on the average, 31.2% of their urines positive for heroin. As can be seen from the data, there is no direct linear relationship of methadone dose with respect to heroin use. Indeed the correlation coefficient was -.017. However, there does seem to be a blocking dose pattern established at the upper end of the dosage scale. Those women receiving 70+ mg/day are more likely

not to be using heroin. In spite of the small number involved, it is highly unlikely that this happened by chance ($p < .001$).

Table III

Methadone Dose (mg)	Number of Patients	Average percent of urines per patient positive for heroin
10-15	9	27.0
20-25	22	31.3
30-35	19	31.2
40-45	18	24.1
50-55	17	34.7
60-65	7	25.4
70+	8	1.8

A totally unexpected finding, presented in Table IV, is the high degree of linear association between the use of diazepam and the daily dose of methadone. Patients receiving 10 to 15 mg/day of methadone had, on the average, 33.9 percent of their urines positive for diazepam. Whereas for those women at the top of the methadone dosage scale, an average of 67 percent of their urines were positive for diazepam. The Pearson Correlation between the two drugs is $r = .84$ ($p < .01$).

TABLE IV

Methadone Dose (mg)	Number of Patients	Average percent of urines per patient positive for diazepam
10-15	9	33.9
20-25	22	36.7
30-35	19	20.6
40-45	18	44.7
50-55	17	52.6
60-65	7	54.1
70+	8	67.3

Discussion

The high level of multi-drug use detected in our population of methadone-maintained women is consistent with that of Chambers (1972) who found, in a one-month study in 1970, that 97% of methadone-maintained patients at Philadelphia General Hospital were using other drugs. This has serious implications of both a phycho-social and biochemical nature. In following the Dole-Nyswander (1965) approach to methadone therapy, once an adequately high methadone dose is given to achieve stabilization, "narcotic hunger" is blocked. Our data, initially, appears to support this blocking dose theory; however, patients on the higher doses of methadone, while not using heroin, are abusing drugs in other categories. It has been suggested (McLellan et. al, 1979) that many patients attempt to induce a particular effect from their multi-drug use. Brill and Chambers (1973) report evidence of an increased level of anxiety in methadone-maintained versus control populations. Perhaps we are seeing diazepam self-medication to alleviate this problem. This would be consistent with our finding of a positive relationship

between methadone dose and diazepam use. There has also been evidence (McLellan et al., 1979) that methadone patients are more depressed than controls. Therefore, we could be seeing amphetamines used as antidepressants. A second factor to consider is the growing number of studies regarding drug interactions between these non-opiate drugs of abuse and methadone. There are two types of interactions to consider. In the first we see an increased level of methadone, or its active metabolites, available at the opiate receptor. In the second, there is a change in the functional response to methadone at its receptor site (Kreek, 1978).

Studies indicate that an interaction of the first type may be occuring with methadone and diazepam wherein we see an increased amount of drug available at the receptor site due to interference in methadone metabolism. Shah and associates (1979) have studied the effect of diazepam on methadone metabolism in mice. They found that diazepam produced significant increases in methadone concentrations in the brain at one hour and in the liver at one and three hours. The enhanced hepatic levels of methadone may indicate an interference in methadone metabolism by diazepam. A number of other studies (Spaulding et al., 1974; Downs, 1979) have corroborated these findings. Although no studies have been done in humans to look at this methadone-diazepam interaction, it is supportive of subjective reports by abusers of the combination. In a self-report study by Bigelow and Liebson (1981) of methadone-maintained women who report diazepam abuse, patients said they generally took their daily dose, all at once, usually within an hour of the time they ingested their methadone. Another report,by Dewey (1972), states that the primary response of patients using diazepam and methadone simultaneously is an increase in the subjective response to the effects of methadone, or a sense of euphoria that was not experienced on methadone alone. These subjective reports are supportive of a biochemical interaction occurring between diazepam and methadone.

The other class of drugs we see frequently abused by our patients is stimulants, most often represented by amphetamines. A drug interaction between opiates and amphetamines was first reported as early as 1944 by Ivy et al. They studied the effect of morphine/dextro-amphetamine combination on pain threshold and sedation in medical students. They found that dextroamphetamines enhanced the analgesic effect of morphine and counteracted,in part, some of its undesirable side effects (nausea and sedation). It was more than 20 years before Evans (1967) followed by Forrest (1977) did supportive work. In 1978, Sprague and Takemari compared analgesic effect of methadone alone and in combination with methamphetamine on mice. They found an enhanced effect when the combination was used. They attempted to further characterize the interaction by measuring brain levels to levels of analgesia. They found that methadone brain levels were not enhanced with methamphetamine pretreatment. Therefore, they suggested that methamphetamine induced changes in neurochemical function which resulted in the enhanced analgesic effect. Richards (1975) studied another aspect of the opiate-amphetamine interaction. His results supported those of other investigators with respect to an increase in methadone's analgesic effect when given in combination with d-amphetamine and are most probably of the

second type: a function of neurochemical events at the receptor level. The conclusions were that amphetamines enhance methadone's analgesic effect and decrease its undesirable side effects.

Summary

Within our study population of 100 women for whom 3,980 urine toxicology reports were accomplished, 98 percent were multi-drug users. This proportion is far greater than would have been calculated from the percent of urines that were positive for the drugs of abuse and is a more realistic estimate of the extent of the problem than is often reported. Despite this high percentage of multi-drug use, due to the uniqueness of our patient population (pregnant women), it is not possible to deny them pharmacologic therapy for their addiction. Therefore, the use of urine toxicology reports in our clinical setting has broader implications than adherence to the methadone regulations. These reports serve as excellent devices to assess newborn abstinence symptomatology, in addition to helping us monitor the physical and psychological status of our patients. The implications are that self-medication may be used to achieve a particular effect concomitant with methadone therapy. The effects are generally to enhance the action of methadone and to decrease undesirable side effects.

Conclusions

Clinicians in the field of drug addiction rehabilitation should take advantage of the requirement of urine toxicology reports for methadone-maintained patients. Particular attention should be paid to those patients who are female, especially during pregnancy or the postpartum period, when psychological issues may be so overwhelming that self-medication appears to be used as adjunct therapy. To assist the clinician in treating such patients, more investigation is necessary to elucidate the psychosocial and biochemical interactions involved with the use of opiate and non-opiate drug abuse concomitant with methadone maintenance.

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How Specific Are the Early Predictors of Teenage Drug Use?

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Early predictors of teenage substance use have now been described in a number of studies. Several of these early predictors have been found across studies that have used different methods, different populations, and different theoretical frameworks.* In the Woodlawn Project we have found several early predictors of substance use. Teacher ratings of early aggressiveness in first grade males (i.e. fighting, breaking rules) was found to be an important predictor of drug, alcohol, and cigarette use, in contrast to shyness (i.e. sitting alone, not speaking up), which was associated in males with later inhibition of substance use. However, shyness in combination with aggressiveness markedly increased the risk of substance use ten years later (Kellam, Brown, Rubin, and Ensminger, In Press 1983; Kellam, Simon & Ensminger, In Press 1983; Kellam, et al. 1980; Ensminger, et al. 1982).

Test performance on readiness-for-school and IQ tests in first grade were also predictive of later drug and alcohol use. Higher scoring first grade children used marijuana and alcohol earlier and had a higher lifetime frequency by age 16 or 17 in the case of both males and females (Fleming et al. 1982; Kellam et al. In Press, 1983; 1980).

This paper addresses the question of how specific these early predictors are to teenage substance use. Other teenage outcomes we have examined thus far include psychiatric symptoms and delinquency. Great importance must be placed on whether these early antecedents are specific to drug use alone, other substances, or whether they are more generally predictive of several, or all of these outcomes. The answers will help us design plausible hypotheses as to the function of these predictors in the developmental paths leading to teenage outcomes.

We have viewed mental health as two dimensional. The first is a domain including affect, self-esteem, and measures of thought disorder. The second dimension is social adaptational status and refers to the adequacy of social role performance by individuals in those particular social fields that are important in particular stages of life (Kellam et al. 1975). For example, the teacher in the early elementary school classroom defines social tasks and rates the behavioral responses of the children to those task demands, just as the foreman does in the work place, parents at home, and significant others in the peer group.

The periodic measures of adequacy by the teacher or other natural raters (as we termed such people) we have called social adaptational status.

Social adaptation is a highly interactive demand/response process. Social adaptational status refers to the level of success attributed to an individual's performance in a particular social field. To review, the predictors we have found in Woodlawn for later substance use all fall into the domain of social adaptational status measures in the first grade classroom. We will discuss the implications of this later in this paper.

Woodlawn is a black, poor, urban community on the South Side of Chicago. Between 1964 and 1968 we made periodic assessments of the classroom social adaptational status and psychological well-being of all first graders in four consecutive cohorts. These assessments were coupled with service and research programs (Kellam et al. 1975) and were supported by a community board composed of leaders from the community's larger citizen organizations (Kellam and Branch, 1971; Kellam et al. 1972).

In 1963, the first year of the Woodlawn project, fifty-seven first grade teachers in the 12 Woodlawn elementary schools were asked to define those behaviors that they thought would indicate that the child was having difficulty accomplishing the tasks of the classroom. Figure 1** contains the social tasks we inferred from the teachers' responses and a representative set of behaviors that the teachers reported to us.

A four point global scale was made for each category of task, ranging from adapting within minimal limits, to mild, moderate, and severe maladapting. Ratings were obtained for each child in the classroom on each task three times in first grade, and again in third grade (Kellam et al. 1975). The Metropolitan Readiness Test was administered early in first grade and an IQ test toward the end of first grade. We consider the tests quasi-social adaptational status measures, since they are school task demands made on the students by the school and are administered to large groups of children with minimal standardization. The reliability and validity of both the test scores and the teacher ratings have been extensively described in earlier publications (Kellam et al. 1975).

In this paper, we examine the long term outcomes predicted by the teacher ratings and those predicted by the test scores. Our study population is the 1966-1967 total first grade population (N=1242), who were followed-up in 1975-1976 when we located and reinterviewed 75% of the mothers of the original students and then reinterviewed, with the parents' permission, 705 of the original children. The children had been 6 or 7 in first grade and were age 16 or 17 at the time of follow-up. Comparisons of the populations of children lost compared to those reinterviewed revealed no differences on any of the measures we are concerned about in this paper.

FIGURE 1: REPRESENTATIVE MALADAPTIVE BEHAVIORS AND SOCIAL TASKS

MALADAPTIVE BEHAVIORS	CATEGORIES OF SOCIAL TASKS
SHYNESS: SHY, TIMID, ALONE TOO MUCH, FRIENDLESS, ALOOF.	SOCIAL CONTACT
AGGRESSIVENESS: FIGHTS TOO MUCH, LIES, RESISTS AUTHORITY, IS DESTRUCTIVE TO OTHERS, DISOBEDIENT.	AUTHORITY ACCEPTANCE
IMMATURITY: ACTS TOO YOUNG, CRIES TOO MUCH, HAS TANTRUMS, SEEKS TOO MUCH ATTENTION.	MATURATION
UNDERACHIEVEMENT: DOES NOT LEARN AS WELL AS HE IS ABLE, LAZY, DOES NOT COME PREPARED FOR WORK, UNDERACHIEVES, LACKS EFFORT.	COGNITIVE ACHIEVEMENT
CONCENTRATION PROBLEMS: FIDGETS, IS UNABLE TO SIT STILL IN CLASSROOM, RESTLESS, DOES NOT PAY ATTENTION.	CONCENTRATION

We will report on outcomes ten years after first grade in three general areas: delinquency; drug, alcohol, and cigarette use; and psychiatric symptoms. All of these data are self-reports by the teenagers. We have reported on the psychometric work dealing with the validity and reliability of the follow-up data elsewhere (Kellam et al. 1980; Kellam, In press, 1983).

The results of the outcome studies generally show that, despite fairly strong correlations among the first grade teacher ratings, the scales have specific and well-defined patterns of outcomes. The following findings are from log linear analyses in which data from all five scales and the test scores were introduced in a sequence of equations testing for 2-, 3-, 4-, and 5-way effects.

Shyness. Shyness among males in first grade has different outcomes depending on whether it is combined with aggressiveness. Among males, shyness without aggressiveness inhibits the later use of marijuana, hard liquor, and cigarettes (Kellam et al. 1980; Kellam, In press, 1983; Ensminger et al. 1982). Similarly, it inhibits later delinquency (Ensminger et al. In press 1983). Shyness in first grade is also associated, however, with a higher level of anxiety in adolescence among males.

Among females shyness is much less significant for later outcomes than for males. The only significant relationship we have found is that early shyness in females inhibits the initiation of use of hard liquor in adolescence (Fleming et al. 1982; Ensminger et al. 1982).

Aggressiveness. For males aggressiveness in first grade leads to increased levels of use of beer or wine, marijuana, hard liquor, and cigarettes, but also a higher level of antisocial behavior ten years later. Those males that are both moderately or severely aggressive and shy tend to have even higher levels of substance use and to some extent delinquency.

For females the outcome of aggressiveness and shy-aggressiveness is quite different. Aggressiveness in first grade does not lead to overt substance use and delinquency in adolescence as in the case of males. However it leads to paranoid symptoms, possibly a form of unexpressed aggressiveness.

Underachievement. Underachievement in first grade predicts clear outcomes ten years later, but not in substance use. We discuss this predictor because of its close and important relationship to first grade shyness and aggressiveness and the test scores.

This very common form of maladaptation leads to higher levels of depressive symptoms but not substance use ten years later among males. Progressively higher levels of first-grade underachievement lead to progressively higher proportion of the sample reporting a high level of depressed feelings ten years later (Kellam et al. In press 1983).

Readiness-for-school and IQ. The two first-grade tests of readiness and IQ are clearly related to drug and alcohol (but not cigarette) use for both males and females (Kellam, Simon, and Ensminger, 1983; Kellam, Brown, Rubin & Ensminger, In Press 1983; Kellam et al. 1980). The higher the children's scores on each test, the higher the lifetime frequency of use. Survival table analyses reveal that the brighter performers start using drugs and alcohol earlier (Fleming et al. 1982).

Among females both IQ and readiness in first grade also had strong relations to psychiatric symptoms 10 year later; lower scores on the first grade tests were associated with higher self-reports of specific symptoms ten years later. Overall distress among females, however, showed a more complex relation: the intensity of teenage distress was highest among the lowest scoring first graders and decreased from the most immature first-graders to the low normal and average group. But the above average group showed considerably more distress than the average. Among males the picture was similar: depression was lower among teenagers who had been more ready for first grade ten years earlier, while anxiety was higher among the above average than the average. It appears that while good performance on first grade readiness and IQ tests may lead to less intense symptoms ten years later, the very highest levels of early performance may lead to later distress.

DISCUSSION

These results show that specific early predictors of drug use also predict the use of other kinds of substances by teenagers as well as certain other kinds of teenage outcomes . These specific maladaptive behavioral responses to first grade tasks have specific and apparently important relationships to outcomes. Aggressiveness in first grade males, for example, predicts heavy drug, alcohol, and cigarette use as well as delinquency. It does not predict these outcomes for females, nor does it predict psychiatric symptoms ten years later for males. Shyness predicts an inhibition of both substance use and delinquency, but also predicts higher anxiety levels in adolescence. Specific patterns also occur for the first grade children's performance on readiness-for-school and IQ tests. Higher first grade scorers use more drugs and alcohol, while low scorers report more symptoms of distress as teenagers, but for the highest first grade scorers the risk of teenage distress increases again.

All of these predictors are behavioral responses rated by the teachers or scored on tests to specific classroom task demands the teacher sets for her children. We have shown in other papers that the maladaptive behavioral responses in first grade operate mainly separately, not as clusters or syndromes (Kellam et al., In press). The single exception is the combination of shyness and aggressiveness, which exaggerates the effects of aggressiveness in predicting substance use and delinquency ten years later among males.

Theoretically, the results suggest that later drug use evolves along developmental paths leading through the specific social task demands and behavioral responses in the first grade classroom or earlier. How children react behaviorally to these demands appears to have long-lasting predictive importance in spite of the great span of time, events, and conditions which intervene between first grade and mid-adolescence.

From the point of view of prevention research, one lesson seems to be that early predictors are an important part of any effort to design specific preventive intervention trials. The kinds of prevention efforts that might reduce the risk for aggressive first graders might very well be counterproductive for the brighter performing children. A second lesson is that sex differences in the developmental paths leading to later outcomes are profoundly important. A third lesson is that the paths leading to drug use in adolescence must be studied side by side with other adolescent behavioral outcomes. Self-reports of psychiatric symptoms, drugs, alcohol, and cigarette use, delinquency, and probably other outcomes, including school achievement and adolescent sexual behavior represent an important profile of outcomes to examine. Studying one outcome in isolation from others loses much information about the meaning and function of the predictors. Indeed, the design of research on development and on preventive intervention should take into account early social adaptational responses, sex differences, and a profile of adolescent behavioral outcomes.

A broad prevention research strategy can be built on a base of life span developmental epidemiological research, the biobehavioral laboratory, and prevention trial research. Models can be constructed as to the functions of early antecedents through epidemiological life span data examined more systematically in the laboratory and prevention trials designed based on the results. Such a strategy would represent a major advance in the next stage of our efforts to understand the origins of child, adolescent, and adult behavior as well as to design and test methods of prevention.

FOOTNOTES:

* See Kellam, Brown, Rubin and Ensminger, In press, 1983, for a review.

** Tables have been left out because of space consideration. Full manuscript and bibliography is available from:

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Increased Effectiveness of Drug Abuse Treatment From Patient-Program Matching

A. Thomas McLellan, George E. Woody, Lester Luborsky, Charles P. O'Brien, and Keith A. Druley

INTRODUCTION

Like many others in the field, our group has attempted to find the patient characteristics that are most related to favorable outcome and then use this information to assign patients to the most appropriate treatments. Initial reports described the design of our matching study (McLellan et al. 1980a), and the evaluation instrument which we developed to provide the admission and six-month followup data for this project (McLellan et al. 1980b). Subsequent studies reported a six-month followup evaluation of 742 alcohol-and drug-dependent patients treated in our six-program network (McLellan et al. 1982), and detailed the patient characteristics which were found to be most predictive of outcome in these programs, based upon retrospective analyses (McLellan et al. in press). In this report, we discuss the results of a prospective patient-treatment matching study that has been employed with a new sample of 476 male, veteran, alcohol and drug abuse patients assigned to treatment in our six rehabilitation programs using these predictors.

RETROSPECTIVE STUDY - Predictors of Patient-Program "Matches"

The retrospective portion of this work involved a sample of 742 male veterans (460 alcohol-dependent, 282 drug-dependent) treated in the six-program Veterans Administration treatment network during 1978. All patients were evaluated at the start of treatment and again at followup six months later, using the Addiction Severity Index (ASI). These data were analyzed to determine if there were any patient-program matches which produced particularly favorable or unfavorable results.

Our initial analyses indicated that a ten-point, global rating of patients' psychiatric severity, estimated at admission, was the single best predictor of most outcome measures for both alcohol- and drug-dependent samples (McLellan et al. 1980b; McLellan et al. in press). This finding prompted us to divide each of the alcohol and drug abuse samples into LOW, MID, and HIGH psychiatric severity groups and perform the predictive analyses again on each of these 6 groups. It is important to note that the psychiatric severity rating is not diagnostic or symptom-specific. It has been shown to provide a reliable and valid general estimate of overall psychiatric/psychological

impairment and is derived from a highly structured interview (McLellan et al. 1980b; McLellan et al. in press). Patients in the LOW psychiatric severity groups (scale values 0-2) were generally asymptomatic with no history of psychiatric problems. MID severity patients (scale values 3-6) generally reported significant symptoms of anxiety, depression and/or confusion but no recurrent history of such problems. HIGH severity patients (scale values 7-9) usually reported pronounced symptoms such as suicidal ideation, paranoia and/or serious confusion/disorientation, and usually had a history of recurring symptoms (LaPorte et al. 1981; McLellan et al. 1981).

Results of this second round of predictive analyses revealed significant relationships which had been masked in the unstratified samples. Alcohol or drug-dependent patients with LOW psychiatric severity at admission showed significant improvement and the best outcomes regardless of which treatment program they entered. Conversely, patients in both samples with HIGH psychiatric severity at admission showed little improvement and uniformly poor outcomes regardless of which program they entered. Thus, for very different reasons, there was no evidence of differential effectiveness from patient-program matching in these groups. Results in the MID severity groups (60 percent of the population) did show evidence for significantly better outcome from patient-program matching, and different, specific factors were predictive in each program.

PROSPECTIVE STUDY - Matched (M) versus Mismatched (MM) Patients

Treatment Matching Strategy - In general, patients in the LOW psychiatric severity groups were recommended for outpatient treatment because this was considerably less expensive and because the retrospective data indicated that approximately equal outcomes would result. The one exception to this strategy was LOW severity patients with significant family and/or employment problems. The original data had suggested that these problems might impair the effectiveness of outpatient treatment, thus an inpatient program was recommended. Patients in the HIGH psychiatric severity groups were recommended for psychiatric treatment at either our inpatient wards or an associated community clinic. The retrospective data had suggested that these patients received relatively little benefit from any of the programs, generally at great expense of staff time and effort (LaPorte et al. 1981; McLellan et al. 1981). However, these patients were treated within the network if no appropriate referral could be made. Patients in the MID psychiatric severity groups were assigned to particular treatment programs based upon the pattern and severity of their other treatment problems at the time of admission.

Patients who were referred or self-admitted to inpatient treatment were screened and assigned to one of the four

specific programs by one author (Druley) using the criteria described. No patient was refused treatment. Only 55 percent of the patients were "matched" to the appropriate treatments. Reasons for not matching included lack of bed availability or treatment slot at the appropriate program (approximately 25 percent), patients' refusal or inability to accept assignment (approximately 13 percent), and simple assignment errors or clinical overriding of the decision strategy (approximately 7 percent). It is important to note that staff members in each of the programs were unaware of which patients were "matched" (M) and which were "mismatched" (MM).

Subjects - Subjects were all male veterans who applied for substance abuse rehabilitation treatment at either the Philadelphia or Coatesville VA Medical Centers during the first nine months of 1980. As in the retrospective study, all patients who completed a minimum of five inpatient days or five outpatient visits were considered eligible. We initially interviewed 649 patients (238 alcohol- and 411 drug-dependent). Approximately 20 percent of each group dropped out of treatment prior to the eligibility criterion. Followup efforts were successful with 94 percent of eligible subjects, leaving 476 patients (178 alcohol-, 298 drug-dependent) with complete data.

Treatment Programs - The substance abuse treatment network of the Veterans Administration in Philadelphia consists of four inpatient (two alcohol, one drug, one combined) therapeutic community programs at the Coatesville VA Medical Center, plus outpatient alcohol and drug abuse clinics at the Philadelphia VA Medical Center. These same programs were studied both in 1978 and 1980. There were changes in personnel during this period with three of the six programs changing their directors. Further, due to construction at Coatesville, there was a move to different quarters for three programs. However, no program changed its treatment orientation or its program length. Space limitations prevent a complete description of these programs; see Gottheil et al. (1979).

RESULTS

Our initial analyses compared the during-treatment performance and six-month follow-up outcomes of the matched and mismatched patients in both the alcohol and drug-dependent samples. The during-treatment comparisons for both samples indicated that the M patients were rated as significantly ($p=.05$ or less) more motivated for treatment, stayed in treatment longer, and had fewer irregular discharges than the MM patients treated in the same programs. Analyses of covariance on the six-month outcome measures, adjusting the groups for admission differences in age, race, prior treatments and the admission criterion score, indicated better outcomes for M patients on 17 of the 19 outcome variables and 10 of these comparisons were significant. In fact, when all followup measures were averaged, the M patients showed 27 percent better outcome than the MM patients.

Excluding High Severity Patients - Although the initial analyses were quite encouraging in both patient samples, it was possible that the results might be accounted for by the greater proportion of patients with serious psychiatric problems in the mismatched group. The results of our retrospective analyses suggested that these HIGH severity patients responded poorly to all of the available alcohol or drug abuse treatments (LaPorte et al. 1981; McLellan et al. 1981). Thus, in our 1980 treatment assignment strategy, we considered the HIGH subsamples to be mismatched in all programs. It was therefore possible that the comparatively poorer performance of the mismatched patients was due largely to the HIGH severity subgroup. We therefore eliminated all HIGH psychiatric severity patients and reanalyzed the data.

Results of these second-level analyses in both the alcohol and drug-dependent samples indicated better adjustment to treatment and better six-month outcomes (adjusted for differences in pre-treatment status) in the matched patients than mismatched patients who were treated in the same programs (see table 1). In the alcohol abuse sample 17 of 19 outcome comparisons were better in the M patients and eight were significant ($p < .05$). In the drug abuse sample all 19 comparisons were better for the M patients and 10 were significant ($p < .05$). Therefore, even without the HIGH psychiatric severity patients, there was considerable evidence for significantly better during-treatment performance and post-treatment outcome (19 percent averaged, across criteria) in the matched patients than in their mismatched counterparts.

Effects of Matching in Four Treatment Programs - Despite the results from the previous two stages of analysis it remained possible that the more favorable results among matched patients might be due to only one or two programs, with less than satisfactory results possible from the other programs. We therefore analyzed during-treatment performance, and adjusted follow-up outcomes for M and MM subjects from each of four programs.

The during-treatment analyses showed that M patients were significantly ($p < .05$) more likely to be rated as appropriate for their assigned treatment in three of the four programs. Further, staff from all four programs rated a larger proportion of matched patients as motivated for treatment.

Analyses of adjusted six-month outcomes indicated considerable evidence of improvement in several areas for both matched and mismatched patients in all four programs. However, comparisons of six-month outcomes between the matched and mismatched groups showed pervasive evidence of better status in the matched patients from all four programs. Only 10 of the 76 comparisons (19 criteria x 4 programs) showed better outcomes for the mismatched patients and only three of these were significant

($p < .05$). In contrast, 66 of the 76 comparisons in the four treatment programs showed better outcomes for the matched patients and 29 of these were significant. Therefore, we conclude that the better during-treatment performance and six-month outcomes seen by the matched patients in the unstratified samples were largely consistent across all the treatment programs examined.

DISCUSSION

Two major findings resulted from the present study. First, the data from both the 1978 and 1980 patient cohorts and for both the alcohol- and drug-dependent samples clearly indicated that substance abuse rehabilitation was effective even without modification of treatment assignment procedures. The impact of this finding was given added weight by the consistency in type, magnitude and distribution of improvements shown by these cohorts in 1978 and 1980 (see McLellan et al. 1982).

A second major finding was that the effectiveness of treatment was improved by matching patients to the most appropriate program within the treatment network. Patients who were assigned and admitted to an appropriate program, based upon the 1978 predictive factors, had significantly better adjustment during treatment, showed more significant improvements and had generally better six-month outcomes than patients who were treated in the same programs but were predicted to have a different optimum treatment assignment (Mismatched patients). In fact, the overall outcome of the matched patients (averaged across all criteria) was 19 percent better than that of the mismatched patients, even when HIGH severity patients were excluded. This "matching" effect was shown in both the alcohol- and drug-dependent samples, in both LOW and MID severity groups and in all of the treatment programs sampled. Thus, the effect was not isolated to a particular type of patient or treatment. This finding indicates that the same factors which were predictive of patient outcome in 1978 were again predictive in 1980. This is noteworthy in view of the poor history of replicated results in treatment outcome evaluations and in view of the changes in the patient population and the treatment program personnel which took place during those years.

Implications - We feel certain that a key reason for the success of the present matching attempt has been the inclusion of a global estimate of admission psychiatric severity as an outcome predictor. In the present study, LOW severity patients showed the best outcomes regardless of their treatment assignment. Because of this, these patients were usually most suited to the less expensive outpatient programs at a savings of more than $53 per patient, per day; or an average of more than $3,700 per patient over the normal course of treatment. Conversely, both the 1978 and 1980 data indicated that HIGH psychiatric severity patients, both alcohol and drug-dependent,

had the poorest outcomes, regardless of the program in which they were treated. In fact, these high-severity patients were more than twice as likely to return to hospitalization (often via the emergency room) than the other patients, during the six-month follow-up interval.

The finding that the substance abuse patients in this population who had more severe employment and/or family problems were less suited to outpatient treatment is logical and consistent with clinical experience. We feel that an extended inpatient rehabilitation program for these patients extricates them from a damaging environment, allows them to concentrate upon the rehabilitation process, and permits the families to objectively re-evaluate their contribution to the patient's condition.

The more specific factors which were associated with favorable outcomes in this study (e.g., medical condition, drug history, etc.) may be peculiar to the particular programs evaluated. We do not contend that these factors are the outcome predictors for other patient samples; only that they were effective in this population, within these programs and at this time. We anticipate that as the programs and/or the patient samples evolve, these more specific predictors may also change. However, we feel that the present methodology will be effective in detecting those changes and that our ongoing "matching" strategy will continue to be helpful in optimizing outcome.

REFERENCES

In the interests of space limitations all references can be obtained from the senior author.

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TABLE 1

SIX-MONTH FOLLOWUP PERFORMANCE OF MATCHED AND MISMATCHED SUBSTANCE ABUSE PATIENTS, EXCLUDING THOSE WITH SEVERE PSYCHIATRIC PROBLEMS

	ALCOHOLICS			DRUG ADDICTS		
	Matched		Mismatched	Matched		Mismatched
CRITERIA[1] N=	80		50	114		142
MEDICAL FACTOR	275	*	350	202	*	248
Days Med. Probs.	9		8	6		7
EMPLOYMENT FACTOR	357	**	437	300	**	471
Days Worked	10		8	12	*	7
Money Earned	350	**	172	469	**	235
Welfare Income	19		26	38	*	64
ALCOHOL FACTOR	217		186	72		80
Days Drinking	7		7	5		6
Days Intoxicated	3		4	1		2
DRUG FACTOR	11	*	33	129	*	153
Days Opiate Use	0		2	5		7
Days Non-Opiate Use	2	*	5	5		6
LEGAL FACTOR	24	**	101	75	*	86
Days of Crime	1		2	3		3
Illegal Income	6	**	32	64	*	132
FAMILY FACTOR	210	*	263	205	*	251
Days Fam. Probs.	2		4	2		4
PSYCHIATRIC FACTOR	121		134	125	*	156
Days of Psych. Probs.	5		6	5		6

[1]All criteria were measured during the 30 day periods preceding admission and preceding six month followup. Higher factor scores indicate greater problem severity.

* = $p < .05$ ** = $p < .01$ by analysis of covariance. Covariates were age, race, prior treatments and the admission criterion score.

A Clinical Profile of 136 Cocaine Abusers

Antoinette Anker Helfrich, Thomas J. Crowley, Carol A. Atkinson, and Robin Dee Post

ABSTRACT

Our examination of 136 cocaine-abusing patients who sought treatment revealed impairment in the following areas: Psychological (99 percent of patients); Interpersonal (87.5 percent); Financial (83 percent); Physical (81 percent); and Vocational (68 percent). Daily dose did, but route of administration did not, contribute to degree of impairment. From these data, we conclude that cocaine's deleterious effects are both physiological and psychological. It appeared to us that maintenance of a cocaine habit is frequently at great expense to the user, regardless of whether the use is intranasal, intravenous, or free-base smoking. In our opinion, it is the multiplicity of psycho-social factors which drives patients to treatment. These factors also define most accurately the extent of consequences associated with cocaine use.

INTRODUCTION

Cocaine use results in significantly impaired functioning for many individuals. Available literature in the area of cocaine abuse focuses on limited aspects of possible impairment. For example, laboratory studies have described cocaine's physical and psychological effects as reported by non-dysfunctional volunteer subjects who are administered doses of cocaine within the prescribed maximal safe dose limits, on controlled schedules, and in controlled settings. Our patients' patterns of cocaine use do not tend to replicate this type of controlled regimen, nor are the effects of their drug administration confined to the actual state of intoxication. Similarly, several studies have solicited subjects who have used cocaine to interview them about cocaine's effects. It is likely that these volunteers were drawn largely from a population of non-dysfunctional, "social-recreational" users. Finally, case studies typically do address the many facets of cocaine abuse, but they report on small samples of users and may focus on atypical cases.

A drawback to what is available in the cocaine literature is that the characteristics and problems of dysfunctional users may not be adequately represented. In fact, conclusions drawn from some of the existing studies may be misleading to individuals who are using the drug as well as to clinicians who are called upon to treat dysfunctional users. An example of misleading information is related to the assessment of severity of cocaine problems based solely on route of administration, i.e., that only intravenous or free-base users become significantly impaired. Risks and losses associated with intranasal administration have been minimized. Van Dyke

and Byck (1982) concluded that intranasal use of cocaine may produce "a pattern of behavior ... comparable to that experienced by many people with peanuts and potato chips." Similarly, Seigel (1977) maintained that intranasal cocaine use "did not tend to escalate to more individually oriented patterns of uncontrollable use." In this study, we investigated characteristics of 136 dysfunctional cocaine users who sought treatment for problems associated with their use. We examined socio-demographic data, patterns of drug use and psychological factors (including symptom presentation) in this group of patients in an attempt to describe the impairment of functioning associated with their cocaine use. We were especially interested in testing the hypothesis that route of administration is correlated with nature, extent and severity of problems. Given a 500 percent increase in the number of individuals seeking treatment for cocaine abuse between 1975 and 1980 (NIDA 1980), it is timely and relevant to examine characteristics of a large sample of cocaine abusers who have sought treatment.

METHODS

The report is based on data obtained from 136 consecutive admissions to specialized cocaine clinics in Denver and Aspen. All patients presented for treatment voluntarily as described in Anker and Crowley (1982). Anyone 18 years or older with a DSM III (American Psychiatric Association 1980) diagnosis of cocaine abuse (pathological use with impairment of social or occupational functioning for at least 1 month) was eligible for admission. Three of the authors (Helfrich, Crowley, Atkinson) treated all patients. Socio-demographic data, drug use information, history of presenting illness, medical and social history were collected at admission. Within two weeks of admission, patients were asked to complete the Minnesota Multiphasic Personality Inventory (Hathaway and McKinley 1967).

The clinicians retrospectively analyzed patient records to compile a checklist with 8 symptom clusters: 1) Major Physical: hepatitis, endocarditis, infections, abcesses, nasal bleeding or ulceration, fainting (loss of consciousness), seizures, respiratory depression and/or failure; 2) Minor Physical: weight loss of 7 or more pounds, insomnia, dizziness, headaches, nausea, tremor; 3) Major Psychological: hallucinations, delusions, serious suicidal ideation; 4) Minor Psychological: depressed, anxious, irritable, guarded, suspicious; 5) Vocational: job loss, impaired functioning at work or school, absenteeism, reprimand or pressure from a supervisor, probation/suspension/revocation of professional license or certification; 6) Interpersonal and Family: spouse or significant other separates or threatens to separate, increased discord; 7) Legal: drug-related investigation, arrest, probation, parole; 8) Financial: diminished or exhausted resources, accumulation of debts.

The Minnesota Multiphasic Personality Inventory (MMPI) is a general survey of psychopathology (Hathaway and McKinley 1967). Scores on three validity scales and ten clinical scales are converted to standard measures (T-scores) for comparison with a normal population. Elevated scale scores (T score $>$ 70) have consistently been associated with behaviorally observable psychopathology.

Because the familiar MMPI scales are highly intercorrelated, we also scored the factor pure measures suggested by Overall et al. (1973). These factor scales are Somatization, Low Morale, Depression, Psychotic Distortion and Acting Out. The Somatization factor correlates most highly with neurotic profiles. Low Morale indicates anxiety discomfort. Depression is self-explanatory. Psychotic Distortion suggests major psychotic disturbance. Finally, psychopathy is indicated by the Acting Out factor.

Hollingshead's two-factor index of social position was calculated for each patient (Hollingshead and Redlich 1958). This index integrates factors of occupation and education. Social class is defined with I being the highest and V the lowest.

RESULTS

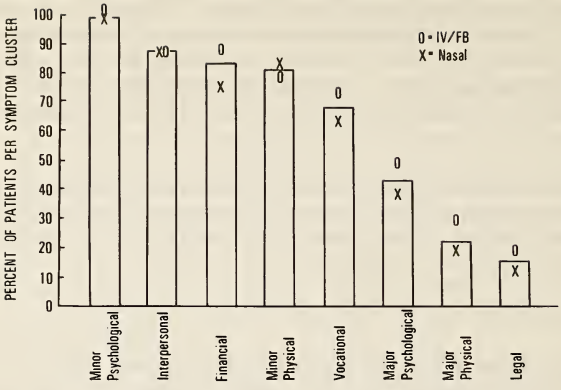
The two cocaine clinics admitted 136 patients between March, 1980 and March, 1982. Thirty females (22 percent) and 106 males (78 percent) had a mean age of 29 years (range 19-57). Forty-two percent were single, 28 percent married, 7 percent separated and 23 percent divorced. Fifty-three percent of patients fell within the top three Social Class continua (median = III). The mean level of education for all patients was 14 years (bi-modal at 12 and 16 years).

Favored routes of administration were: intranasal, 57 percent of patients; intravenous, 33 percent; free-base smokers, 10 percent. We converted average doses estimated by patients at the time of admission to grams-per-week. The mean dose for the total group was 8 grams per week (range .25 to 45 grams per week). The mean dose for the nasal group was 7.2, for the IV group it was 8.5 and for the free-base group, 10.3; these differences were not significant by analysis of variance ($F = 1.52$). Seven percent of patients reported using cocaine less than twice per week, 30 percent used two or more times per week, 15 percent used two to three times daily, 27 percent used more than three times daily and 18 percent reported binge use. Patients averaged 5 years between first use and admission to treatment (range = 1-20).

Of these patients, 40 percent reported dysfunctional use of no other drugs, 34 percent were concurrently abusing alcohol, 8 percent reported problematic marijuana abuse, 5 percent reported amphetamine abuse and 5 percent abused tranquilizers. Only 4 patients were using opiates (including synthetic opiates).

Clinically, a pattern of significant psychological distress emerged. Analysis of the symptom checklist revealed that 85 percent of patients presented four or more of the eight symptom groups. The mean number of symptom clusters presented was 5. The number of symptom clusters reported by each patient did vary significantly (ANOVA, $p > 0.02$) with route of administration, but the difference was small (mean number of symptom groups presented per patient in nasal users, 4.7; in IV/FB users, 5.3) and of questionable clinical importance. The percentage of patients representing each symptom complex are listed below: 1) Minor Psychological - 99%; 2) Interpersonal - 87.5%; 3) Financial - 85%; 4) Minor Physical - 81%; 5) Vocational - 68%; 6) Major Psychological - 43%; 7) Major Physical - 22%; 8) Legal - 15%. (See Figure 1). Figure 1 illustrates that route has little effect on specific symptom clusters; chi square tests of these differences were not significant.

FIGURE 1



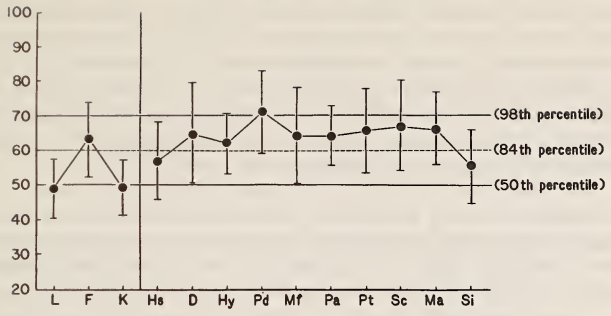
Frequency of symptom clusters reported by patients at admission
o = Frequency for the IV and free-base group
x = Frequency for the Nasal group

Patients' dose estimates correlated significantly ($r = .34$; $p = .00003$) with number of symptom clusters per patient at admission. As dosage increased, so did the number (range) of symptom clusters reported. However, the presence or absence of Major Physical symptoms was the only cluster that was significantly related to dose estimates ($F = 7.85$, $p > .01$). It is interesting to note that symptom clusters correlated with dose for the nasal group ($r = .49$), but there was not a significant correlation between dose and symptom clusters in the IV/FB group.

Seventy-six patients completed MMPI's; others left treatment early or refused to complete the test. The generally elevated mean T-scores corroborate the symptom information presented above documenting that psychological turmoil is clearly evidenced by this group. (See Figure 2). A comparison of mean MMPI factor scores (Overall et al. 1973) between this group of cocaine abusers and normals also suggests considerable psychological turmoil. The Acting Out factor was especially elevated with a mean for the cocaine group that was greater than one standard deviation above the mean reported by Overall et al. for normals.

We found no significant relationships between elevated MMPI scale scores and route of administration. In other words, it did not appear that IV/free-base users differed from nasal users along MMPI dimensions. ANOVA F ratios for each MMPI scale by route of administration were uniformly insignificant.

FIGURE 2



Ordinate: MMPI T-scores
Abscissa: MMPI Scales

We correlated each patient's dose estimates with each scale of the MMPI. Considering all subjects from whom MMPI's were available (N = 76), only two significant correlations appeared (scales F and Pd). F scale elevations are associated with rebellion, unconventional thinking and severity of illness in a clinical population. Pd scale elevations suggest social alienation, rebellion and resentment (Carson 1969) and has been correlated highly with substance abuse (Caldwell and O'Hare 1975). The interpretation of increased probability of substance abuse is corroborated by a mean MacAndrew's scale score of 25; the cutoff used to predict alcohol abuse is 24 (MacAndrew 1965). While statistically significant, the correlations are modest (r = .22 and r = .21, respectively). They tentatively suggest that increased dose may be associated with greater rebelliousness, social alienation, anger and psychiatric dysfunction.

DISCUSSION

This sample of 136 cocaine patients exhibited significant and serious psychological distress regardless of the route of cocaine administration. A general inventory of psychopathology (MMPI) revealed mean scale scores that are clinically elevated (> one standard deviation above the norm) on 9 of 13 scales. In terms of symptom presentation at admission, the range and severity of reported dysfunction challenge reports of cocaine's benign effects. Given that over half of our sample were intranasal users, we were especially interested in examining the hypothesis that intranasal use is relatively safe compared to intravenous use or free-base smoking (Van Dyke and Byck 1982; Wesson and Smith 1977). Additionally, we questioned whether classifications of patterns of cocaine use (i.e., dose regimes) might be a misleading distinction. For example, every patient in this sample began with experimental use; some only months before admission. Using Seigel's (1977) method of classifying intranasal cocaine users, many of our sample would be considered "social-recreational" users. However, unlike Seigel's sample of interview subjects for whom "psychometric instruments failed to detect the presence of dysphoria or psychosis," our patients clearly demonstrated adverse consequences even with doses as small as $\frac{1}{4}$ gram per week.

We investigated characteristics of 136 patients for whom dysfunctional use of cocaine was self-diagnosed by their voluntary admission to treatment. The socio-demographic profile differs from NIDA's characteristics of cocaine abusers admitted to treatment programs (1977) in several respects. Our patients were older ($\bar{x}$ = 29); more educated ($\bar{x}$ = 14 years); employed (80 percent); predominantly white (90 percent); and had fewer legal complications (15 percent). We had fewer intranasal users (57 percent vs. 69 percent) and our patients used cocaine more frequently (7 percent vs. NIDA's 54 percent used cocaine once per week or less).

Maintaining distinctions among routes of cocaine administration in terms of adverse consequences may be somewhat deceiving in the assessment of the overall clinical profile. It is true that greater blood plasma concentrations of cocaine result in more noticeable physiological and psychological effects during intoxication and that intravenous or free-base smoking lead to peak concentrations more quickly. Due to these factors, abuse potential and threat of overdose are more likely. Based on this observation, however, much of cocaine research to date assumes that impairment, extent of adverse effects and dangerously frequent use are mainly a function of the route of administration (Van Dyke and Byck 1982). The percentage of nasal users in the general population whose functioning is impaired may be much lower than the percentage of impaired IV/FB users. It is important to emphasize, however, that in our experience, intranasal users do present clinical syndromes. In fact, there was no significant relationship between MMPI scale elevations and route of administration in an analysis of variance. Dose also was not significantly correlated with route. Finally, chi square computations for each symptom cluster by route were not significant, even though route was marginally associated with the total number of symptoms reported. In summary, route of administration did not appear to affect dose, MMPI scores, or specific types of symptoms in this clinical population. Nasal and IV/FB groups of patients were clinically indistinguishable.

Dose, on the other hand, is related to the number of symptom clusters reported by each patient at admission and to elevations on the MMPI F and Pd scales. With increasing doses, patients are more likely to report Major Physical symptoms. The MMPI findings suggest that dose does correlate with overall severity of illness and are consistent with Post's (1975) assertion that "increasing the dose and/or chronicity of cocaine administration is associated with increasingly severe affective and cognitive alteration".

Besides the direct (primarily pharmacological) effects of cocaine use, there are numerous, more insidious, and presumably more pervasive consequences that are not adequately addressed in laboratory research. Because of the potency of cocaine's reinforcing effects, animals will work, even to the point of death, to receive injections (Deneau et al. 1969). The possible parallel for human beings is of considerable clinical concern. Cocaine drives behavior toward continued and exaggerated patterns of use. Our patients report being drawn into a compelling cycle of obtaining, using and recuperating from cocaine use. They maintain that cycle despite serious risks (physical and psychological) and losses (spouse, job, finances, etc.). It is this series of risks and losses which eventually leads patients into treatment because they are experiencing serious psychological distress.

Many factors could have contributed to the psychological turmoil in this sample of cocaine abusers (as evidenced by reported symptoms and elevated MMPI scales). It may be that these patients were predisposed to psychopathology and cocaine use triggered a more intense reaction, but their progress in treatment and history of pre-morbid adjustment argue against this hypothesis. Perhaps the psychological turmoil is directly related to the pharmacological action of cocaine. However, given the short duration of cocaine's effects and the time lapse between dosing and admission, it is unlikely that direct effects would have contributed, for example, to elevated MMPI scores. In addition, we found no relationship betwen route of administration and either dose or clinical data (symptoms, MMPI). Finally, it may be that the social and psychological consequences of increasing cocaine use create and maintain serious psychological stresses. Eventually the individual's overall level of functioning is significantly impaired. None of these possible explanations can be discounted; however, we feel that the third is the most plausible and of the greatest clinical importance.

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Cocaine and Amphetamine Dependence Treated With Desipramine

Forest S. Tennant, Jr., and Richard A. Rawson

ABSTRACT

Desipramine was administered to 8 amphetamine- and 14 cocaine-dependent persons to assist withdrawal. Nineteen of 22 (86.4%) reported discontinuation of drug use within two to seven days, of which 15 (68.2%) gave urine samples negative for amphetamines or cocaine. Recent primate studies show that chronic methamphetamine administration markedly depletes brain norepinephrine, which suggests that desipramine is probably effective in treating amphetamine and cocaine dependency because it selectively blocks norepinephrine uptake.

INTRODUCTION

No specific treatment has been identified for amphetamine and cocaine dependence. (1,2) Consequently, attempts to treat these conditions have met with dismal outcome. (3,4) For example, Anderson, et. al. offered 18 amphetamine users psychotherapeutic treatment, but no patient returned for even a single, scheduled visit. (3)

Animal studies suggest a possible treatment for amphetamine and cocaine dependence. (5,6) Although Axelrod (7) demonstrated in 1961 that amphetamines and cocaine block the uptake of norepinephrine, Seiden, et. al. have only recently shown that chronic methamphetamine administration depletes appoximately 30 to 50 percent of whole brain norepinephrine in primates. (5) Therefore, the chronic cocaine and amphetamine user may be in a condition of severe norepinephrine depletion.

The tricyclic anti-depressant desipramine produces a greater degree of selective blockage of norepinephrine uptake than any other tricyclic anti-depressant. (8) Based on this, we hypothesized that humans dependent on amphetamines and cocaine could be treated by administering desipramine. Reported here are our initial findings with 14 cocaine- and 8 amphetamine-dependent patients.

METHODS

During 1981-1982, subjects sought treatment at four outpatient clinics located in East Los Angeles County. All stated they compulsively used amphetamines or cocaine multiple times each day for at least three months and that they were unable to cease use without some form of medical intervention. Although some patients used alcohol or marijuana occasionally, none considered any drug a problem except amphetamines or cocaine. The treatment team consisted of a physician, nurse, and psychologist. Each subject completed a written questionaire which inquired about length and amount of drug use, source of drugs, health problems, previous attempts to cease drug use, and symptoms which precluded cessation of drug use. A complete physical examination and urine analysis for amphetamines or cocaine were done. The first day's dose of desipramine was 25 mg. given two to four separate times for a 24-hour total of 50 to 100 mg. Subsequent days' dosage was dependent on withdrawal symptoms. Patients were informed they could take desipramine for as many days as it proved helpful in achieving amphetamine or cocaine abstinence. They were instructed to return to the clinic daily for the first five days and after this period to attend one to two times weekly for up to one month.

A daily drug diary was kept by each patient which listed the time of day and amount of desipramine, amphetamine, cocaine, or other drug used. On each visit, patients were asked about continued amphetamine or cocaine use and whether desipramine helped them cease drug use; reduced drug craving; prevented depression and apathy; and reduced insomnia, since these symptoms are well-recognized as part of amphetamine and cocaine withdrawal. (1,2) A repeat urine test for amphetamine or cocaine was taken in the second week of treatment. When the patient chose to discontinue desipramine, the option for weekly counseling sessions with the psychologist was offered. Patients who left treatment were interviewed by telephone approximately 30 to 45 days after leaving treatment to help determine if relapse had occurred.

RESULTS

The majority of amphetamine users were white, unmarried, employed, and female, while cocaine users were predominantly employed males. (See Table 1) Duration of amphetamine dependence ranged up to 15 years and cocaine dependence up to 8 years. All patients except one cocaine user returned to the clinics for multiple visits. Seven of eight (87.5%) amphetamine and 12 of 14 (85.7%) cocaine users reported they ceased drug use within two to seven days after beginning desipramine administration. Other than one amphetamine user who stated that desipramine wasn't helpful and took it only for two days, the remaining amphetamine users chose to take it for period ranging from four to 120 days (mean of 35.5). One amphetamine patient has chosen to maintain on desipramine for a period that now exceeds 120 days, and another took it intermittently for 105 days. Cocaine users tended to take desipramine for shorter periods. Only three cocaine patients elected to take desipramine for longer than 7 days with

the longest period being 52 days. Eleven took desipramine for 2 to 7 days, and 9 of these patients stated they ceased cocaine use and declined further treatment. Urine test analysis for documentation of cocaine cessation could only be obtained in eight cocaine users due to the claims that further treatment was unnecessary and failure to attend the clinic for more than one week.

Subjects variously reported that desipramine helped reduce drug craving, prevent depression and aid sleep. (See Table 1) Daily doses of desipramine ranged from 50 to 125 mg. per day. Patients reported it to be most effective when taken in multiple doses of 25 mg. two or three times during the day and a dose of 25 to 50 mg. at bedtime. The side-effect reported was mild sedation in two patients. One amphetamine and two cocaine users reported that desipramine suppressed amphetamine or cocaine effects when they attempted to use them.

DISCUSSION

Although this study was conducted on a non-blind basis with a relatively small number of subjects, the results are impressive compared to previously published reports by us and others who have attempted to treat amphetamine-dependent patients on an outpatient basis. (3,4) We cannot identify any published reports of systematic attempts to treat and assess outcome of cocaine-dependent persons. (1) The major difficulty in treating amphetamine users has been the inability to retain patients in treatment beyond the first clinic visit. In this study, all 22 patients were retained beyond the first clinic visit. Nineteen of the 22 (86.4%) reported cessation of amphetamine or cocaine dependence within two to seven days, and it was possible to document conversion of urine from amphetamine or cocaine positive to negative in 15 of these subjects.

Use of desipramine to treat amphetamine and cocaine-dependent persons represents a significant departure from conventional drug withdrawal therapy. (4) In addition, it uses a tricyclic anti-depressant in a way not previously utilized. (8) Until now, pharmacologic assistance has normally only been used for drugs such as opiates, barbiturates, and alcohol that produce physical dependence. (4) In this preliminary study, desipramine was utilized for withdrawal from drugs which do not produce typical physical dependence. (1,2) The basis for the use of desipramine was to enhance norepinephrine activity, since recent studies in primates show that chronic methamphetamine administration significantly depletes whole brain norepinephrine. (5,6) Normally, desipramine and other tricyclic anti-depressants require approximately three weeks to show clinical improvement of endogenous depression which has led to the belief that they act to relieve depression by a mechanism not totally related to neurotransmitter blockage. (8,9) Subjects in this study reported immediate effects of desipramine which were most likely related to its ability to selectively block norepinephrine uptake and potentiate

norepinephrine activity.

The animal studies by Seiden et. al. showed that norepinephrine depletion may be irreversible following long-term methamphetamine administration. (5) If this is the case in some humans who abuse amphetamines chronically, it provides an explanation for the intractable nature of amphetamine dependence as well as an explanation why some subjects in this study voluntarily chose maintenance with desipramine. Unfortunately, there is no reliable method at this time to directly measure whole-brain norepinephrine in man.

This study must not be over-interpreted due to its non-blind nature, the possibility of placebo effect, and the inherent difficulty to control drug-dependent research subjects. Further clarification of the role of desipramine in the treatment of amphetamine and cocaine dependence must await double-blind trials.

TABLE ONE

CHARACTERISTICS AND OUTCOME OF
AMPHETAMINE AND COCAINE SUBJECTS

	Amphetamine N=8	Cocaine N=14
Age Range	19 - 39 years	22 - 36 years
Mean Age	29.0 years	26.9 years
Females	6 (75.0%)	4 (28.6%)
White	8 (100.0%)	14 (100.0%)
Employed	7 (87.5%)	10 (71.4%)
Married	1 (12.5%)	8 (57.1%)
Range Drug Consumed Each Day	3 to 40 tabs/ caps	1/2 to 3 gms
Total Length of Drug Use (Mean)	8.4 years	3.4 years
Length of Time Desipramine Administered (Range)	2 - 120 days	2 - 52 days
Length of Time Desipramine Administered (Mean)	35.5 days	11.9 days
No. Reported Cessation of Drug Use	7 (87.5%)	12 (85.7%)
No. With Two or More Clinic Visits	8 (100.0%)	13 (92.9%)
No. Converted Urine From Positive to Negative	7 (87.5%)	8 (57.1%)
No. Reported Desipramine Did Following:		
Helped Cease Drug Use	7 (87.5%)	12 (85.7%)
Reduced Craving	2 (25.0%)	8 (57.1%)

Prevented Depression	5 (62.5%)	6 (42.9%)
Helped Sleep	5 (62.5%)	2 (14.3%)

Patient Status 30 - 45 Days After Admission:

Desipramine Maintenance	2 (25.0%)	3 (21.4%)
Reports Total Abstinence	2 (25.0%)	4 (28.6%)
Relapse to Drug Use	3 (37.5%)	2 (14.3%)
Unknown	1 (12.5%)	5 (35.7%)

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Recreational Opiate Addiction in a Dentist and a Nurse

William E. McAuliffe

This article presents case studies of a new form of opiate abuse in medical professionals that appears to be on the rise in the United States. Medical professionals have long had high addiction rates because of their easy access to drugs (Terry and Pellens 1970). Until recently these addictions have almost always been therapeutic (iatrogenic) or quasi-therapeutic in origin (Clark, 1962; Winick, 1961; Green et al., 1978; Modlin and Montes, 1964; Wall, 1958; Pescor, 1942; Poplar, 1969). Therapeutic addictions originate from treatment with opiate medications for pain; quasi-therapeutic addictions stem from opiate self-treatment of depression, anxiety, fatigue, stress, hangover, and so on; nontherapeutic addictions result from recreational euphoria-seeking. The reasons physician and nurse addicts have given most often for their opiate abuse are physical pain, marital problems, stress, alcoholism, insomnia, and fatigue from overwork (Winick, 1961; Green et al., 1978; Modlin and Montes, 1964; Wall, 1958; Jones, 1958; Pescor, 1942; Poplar, 1969). Modlin and Montes (1964) found that 10 of 25 physician addicts were initially prescribed opiates by a physician or surgeon, and then continued by self-prescription. There is little evidence that in the past medical professionals used opiate drugs for kicks. Winick (1961; 1974) found that 98 physician addicts mentioned euphoria sixth in order of frequency as a reason for current use of opiates, whereas 195 nurse addicts did not mention euphoria at all. In other studies physician addicts did not mention euphoria-seeking as a reason for drug use (Green et al., 1978; Jones, 1958; Wall, 1958; Modlin and Montes, 1964).

However, the incidence of nontherapeutic addiction among medical professionals may soon increase substantially. Unlike previous decades, today many young medical professionals have been exposed to and have used drugs recreationally. My colleagues and I recently surveyed samples of premedical students, medical students, nursing students, and young physicians in New England to find that between 56 percent and 71 percent have used marijuana and that significant proportions have progressed to recreational experimentation with higher-risk drugs, especially cocaine

NOTE: This paper was presented at the 1981 Scientific Meeting.

(between 15 percent and 26 percent) (McAuliffe et al., 1982). It is not surprising therefore that impaired physician committees have begun to see a new type of physician addict, one who is addicted to recreational drugs, such as marijuana and cocaine (U.S. Journal, 1981, p.10; Warmkessel, 1981; Buys, 1982, p. 10; Grosswirth, 1982). Of 52 physicians recently referred to California's impaired physician program, 28 percent had problems with cocaine and 13 percent with marijuana (Buys, 1982). The present author recently surveyed eight specialists who treat impaired physicians, and they reported that a median of 10 percent of the 230 addicted physicians they have collectively treated were nontherapeutically addicted.

The present article describes two case examples from a sample of eight the author has interviewed over the past three years. Although numerous case histories of therapeutically or quasi-therapeutically addicted health professionals have been published, the author knows of no published case histories which purport to describe nontherapeutically addicted health professionals. Since there appear to be important differences between the types, these case examples should be valuable for both clinicians and researchers.

METHODS

The case studies stem from tape recorded, structured interviews with an addicted dentist and nurse. Both subjects were receiving treatment for drug addiction, one in a therapeutic community (drug free, in-patient program) and the other on an out-patient methadone maintenance program. The interviews covered family background, drug use history, and consequences of addiction.

RESULTS

Case #1, The Dentist

This 29-year-old dentist began experimenting with opiates and other drugs while taking a pharmacology course during his second year in dental school. Fascinated with the drugs he was learning about, he and two classmates, who were more experienced recreational drug users than he, would try the drugs (alium, methaqualone, barbiturates, Demerol, and codeine) they discussed in class. Up to then, the subject had smoked marijuana daily while in college, tried mescaline a few times, and cocaine and amphetmines just once each. After six months of experimentation, he tried Percodan and immediately strongly preferred its effects over the other drugs he had tried. By his last month of dental school, he was taking codeine or Percodan orally (8 to 16 tablets at a time) twice a week. On graduation, he stopped completely until the next fall when he took a job in a very remote area where dispensing of psychoactive medicines was not closely regulated. During that winter and spring his solitary use of codeine became more and more frequent so that he was psychologically ad-

dicted by May and experienced physiological withdrawal symptoms during his summer vacation. Euphoria-seeking was a major reason for his use of opiate drugs, his drug use patterns, and his drug preferences.

He remained addicted, mainly to Percodan, for the next three years. During that period, his usual mild manner gave way to bouts of rage in which he frequently yelled at assistants and even abused his wife, both physically and psychologically. His dosage escalated to as many as 25 Percodan tablets per episode. He overdosed once, had a major automobile accident when drug intoxicated, and twice "nodded out" while treating patients.

He finally sought long-term treatment after pressures began to build from all sides. At first he and his wife tried unsuccessfully to cope with his addiction by moving, his changing jobs several times, seeking private psychiatric care, and then detoxifying briefly in a private substance abuse hospital. On relapse, his drug use and prescription writing became more frequent, and soon he began having to travel long distances to obtain drugs because local pharmacists refused to fill his prescriptions. He also collaborated for several weeks with a street addict who had approached him for a prescription: each day the addict would pick up a prescription, get it filled, and return half of it to the dentist. This episode was his only contact with street addicts except through treatment programs; he never adopted subcultural drug use patterns but admitted contemplating intravenous injections after talking to street addicts who were fellow patients at the drug programs. His wife left him, and his family refused to see him. The Drug Enforcement Administration removed his narcotics prescribing privileges, and at the urging of a dental society representative, he entered a 28-day detoxification program. He quickly relapsed on release, was arrested for trying to fill a prescription, and entered a therapeutic community (inpatient, drug free facility) on the advice of his probation officer. At last report he had successfully completed a year's residence, had returned to dentistry part-time, and "graduated" from his drug treatment program.

Case #2, The Nurse

This 30-year-old nurse began heavy recreational use of drugs (marijuana, hallucinogens and amphetamines) as a teenager in a lower-middle-class family. She became addicted to amphetamines. She tried heroin and other opiates with friends at age 17, and within two years was addicted. After several years of opiate addiction, during which she became a drug dealer and then a prostitute, she was arrested for selling narcotics and was placed on probation. Despite continued occasional (mainly weekends) opiate use, she enrolled in a junior college, achieved top grades, and then entered nursing school. Her opiate use increased in frequency during her last year in nursing school (she frequently took examinations while under the effects of heroin), so that her

grades declined from "A's" to "C's". As a registered nurse, she began intravenously injecting the narcotics available to her (replacing opiates taken from vials with saline solution) and within a year was addicted to Dilaudid. She would occasionally buy street drugs from close friends. Her dosage had escalated to as much as 36 mgs. of Dilaudid in one injection. She overdosed (injecting 1,000 mg. of Demerol) in the bathroom at work, sustained minor head injuries, and lost her job, although the director of nursing offered to help the subject and did not report the subject's addiction to authorities. For several weeks, the subject depended on street drugs exclusively (up to then she had used them only on weekends when professional supplies were not available), and then was accepted into a methadone-maintenance program. During the last five years she worked as a nurse in nursing homes and in a general hospital, while on methadone. She has used illicit opiates (obtained from work or the street) only on rare occasions when she missed her methadone dose. Recently, she detoxified from methadone, but soon relapsed to using drugs available at work and on the street. She is now back on methadone.

The nurse was asked about the reasons for her opiate use:

Interviewer: Would you say that your opiate use was more a form of recreation, or a form of self-treatment for some sort of problem?

Subject: Recreation

Int: Were there times when you felt that you . . .

Sub: It became a self-treatment for withdrawal symptoms, but I don't really think that's what the question is saying.

Int: No, We're looking more for physical pain or some sort of emotional problem--taking the drug to bring yourself back up to some sort of par. You're talking about taking the drug to move yourself away from some sort of par towards more of a euphoric effect.

Sub: Yes.

Int: Were there ever times that you remember taking drugs principally because you were so down you took the drug to bring yourself back up to just a tolerable level?

Sub: There may have been times when I thought like that, but I can't really see it being that way.

Int: It was more of a recreational use straight through?

Sub: Yeah.

Int: And would that have been true, that particular pattern of recreational use, as opposed to a therapeutic use? Did that pattern maintain from early drug taking then moving on into when you were in a more medical profession?

Sub: Uh-huh (yes).

Int: So it was always . .

Sub: Even when I didn't have a habit I would like to go out on a weekend and get high first. Stuff like that. We were always into getting or obtaining drugs before concerts or going to a club or doing something in particular. Y'know?

DISCUSSION

Interviews with these two subjects revealed several important differences between them and opiate-addicted health professionals described in previous studies. These subjects began using opiate drugs recreationally with friends, after several years' heavy use of marijuana and other nonopiate drugs. The usual addicted health professionals began opiate use latter in life, by themselves, with little or no prior drug-use history, and as a means of self-treatment rather than recreation. The dentist began using in dental school, and the nurse had already been addicted before entering nursing school. These patterns of initiation were observed in other nontherapeutically addicted health professionals, but contrast sharply with patterns described by therapeutically addicted physicians and nurses who began use after years in their professions.

Addiction adversely affected the careers of the dentist and nurse, and almost took their lives. Despite their medical knowledge of dosages and the use of pure drugs, both subjects overdosed and had occasions in which they "nodded out" while caring for patients. Both subjects also experienced accidental injuries due to being intoxicated on opiates. They explained their large doses by their desire for deep euphoria.

Finally, the dentist and nurse were unique because they obtained forms of drug treatment, methadone maintenance and therapeutic community, that are popular for nontherapeutic street addicts but not for therapeutically addicted health professionals. Perhaps because most addicted health professionals begin opiate use as self-treatment for medical or psychiatric problems, it is reasonable that they seek and respond to medical detoxification and psychiatric treatment for their drug problems. By contrast, nontherapeutically addicted health professionals may instinctively recognize their similarity to street addicts and therefore seek

long-term drug treatment such as therapeutic communities, designed to change values and lifestyles. If so, impaired health professionals committees, who refer addicted professionals for treatment and oversee their progress, should nowadays pay close attention to whether the health professional was therapeutically or nontherapeutically addicted.

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Frequency of Reinforced Practice in the Development of Tolerance to Alcohol

D. J. Beirness and M. Vogel-Sprott

Recent investigations have demonstrated that practice of a task in the drug state facilitates the development of alcohol tolerance. The present study explored the development and subsequent display of tolerance as a function of the frequency of reinforced practice under alcohol in social drinkers.

Three groups of four males each learned a complex psychomotor task to a stable level of performance. They subsequently performed either 4, 8 or 12 task trials under a moderate dose of alcohol during each of five separate drinking sessions. During the first four drinking sessions, Ss were reinforced for task performance which equalled the S's drug-free level of achievement. All Ss performed without reinforcement on the fifth drinking session.

All groups developed tolerance, evidenced as a significant decrease in drug-induced impairment of performance over the first four drinking sessions. The final level of tolerance displayed was greatest for Ss who performed 12 task trials on each session under alcohol and least for Ss who performed only four trials. When reinforcement was withdrawn, the amount of impairment returned to that observed on the initial drinking session.

These findings indicate that more frequent reinforced practice under alcohol facilitates the rate of acquisition of tolerant behaviour. In addition, the potent effect of reinforcement in the display of tolerance is illustrated by the "extinction" of tolerance when the reinforcement was withdrawn. Taken together, the results are consistent with a learning interpretation of tolerance.

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Urinary Homovanillic Acid Methadone Withdrawal

Frank A. DeLeon-Jones, John M. Davis, Edet E. Inwang, and Haroutune DeKirmenjian

Homovanillic acid (HVA), the main metabolite of dopamine, was determined in urine of long-term methadone-dependent subjects. Two separate studies were performed. The first study was designed to assess the effects of gradual methadone discontinuation in eight subjects who received stable methadone doses ranging from 40 to 60 mgs daily per subject for a two-week stabilization period followed by a stepwise decrease of 10 mg/week until zero dose was reached. Ratings of withdrawal symptoms were done twice daily and 24-hour urines were collected throughout the study. The second study was designed to assess the effects of abrupt methadone withdrawal in fifteen long-term methadone-dependent subjects. Each subject was stabilized on a 40 to 60 mg daily dose of methadone for two weeks following which methadone was abruptly discontinued. Withdrawal ratings and 24-hour urine collections were done during the entire study period. Urine samples were also obtained from a healthy control group. HVA levels during the stable methadone period were not significantly different from those of healthy controls. The gradual withdrawal study as well as the abrupt withdrawal study showed a significant decrease in urinary levels of HVA during withdrawal relative to the stable methadone period and to the HVA excretion by normal controls. These data will be discussed in comparison to the urinary excretion of MHPG, normetanephrine, metanephrine and cyclic AMP by the same subjects as well as platelet adenylate cyclase activity during stable methadone and withdrawal by some of these subjects. Also these findings will be discussed in relation to animal work which relates to the role of dopamine and norepinephrine in tolerance and physical dependence.

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Brain Growth and Cerebral Ventricular Development in Newborn Infants of Drug-Dependent Mothers

Matthew E. Pasto, Pamela M. Foy, Leonard J. Graziani, Barry B. Goldberg, Elizabeth D. Leifer, and Loretta P. Finnegan

Various investigators have been concerned about the incidence and severity of neonatal abstinence. Clinical symptomatology and its management have been evaluated. However, despite concerns and continued queries about the pathophysiology of the syndrome, few studies have evaluated the effects of maternal prenatal drug intake on the developing brain. One investigator (Tenner, 1976) has documented abnormalities in the ventricular systems of children of drug-dependent women. Tenner reported compression of the cerebral lateral ventricles in an a-mode ultrasound study of passively addicted and symptomatic neonates. However, no control subjects were evaluated. Left ventricular compression, with the third ventricle shifted to the right, was found more commonly than right or bilateral compression. In a limited followup study, the ventricles remained small in some infants for as long as 2 to 14 weeks. The cause of the compressed ventricles was undetermined, but the authors conjectured that cerebral edema might be responsible.

Few investigators of perinatal addiction have utilized objective measures, particularly due to the lack of methodology and the nature of the subjects. Therefore, ultrasound methodology was considered and chosen with attention to the relative risks and benefits to the newborn. The American Institute of Ultrasound Medicine has categorically stated that there have been no independently proven harmful effects of ultrasound intensities of 100 mW/CM^2. The high resolution 5 megahertz scanner in use in the present study has an intensity rating of 16 mW/CM^2. The only contact with the infant is the transducer and ultrasonic coupling gel or mineral oil applied to the baby's head. There is no need to exert pressure on the head nor restrain the infant. Many times the scanning can take place while the infant is feeding or sleeping. Because the equipment is portable and the transducer is hand held, the examination can be performed in the nursery without removing the infant from the crib or isolette. Therefore, benefits obtained by the study are derived at minimal risk.

The ATL Mark 100 sector scanner is a high resolution real-time scanner that enables us to scan through the fontanel and sutures and obtain detailed visualization of the brain. Since we are able

to scan through the fontanels we can see the lateral ventricles in the coronel scanning plane as well as the parasaggital scanning plane by turning the transducer 90 degrees to the coronal plane. The only limitation to scanning is the naturally occurring closure of the anterior fontanel in the mid to late first year of life. The brain is imaged through the anterior fontanel with a 90 degree sector field of view. Ultrasound visualizes changes in tissue texture and tissue boundaries. Hence, the cerebral sulci are very well seen in the interhemispheric fissure. The margin of the lateral ventricles and the superior margin of the corpus callosum are well defined. The Sylvian fissures can be seen laterally on either side. Also, because the examination is real time, arterial pulsations can be visualized in both branches of the anterior cerebral arteries in the interhemispheric fissure. Figure 1 is a parasagittal scan of a lateral ventricle, demonstrating the frontal horn and the body and atrial regions. The choroid plexus can be seen lying on the floor of the body of the lateral ventricle and extending along the posterior aspect of the thalamus within the atrium. Figure 2 demonstrates a normal coronal scan through the region of the ventricular atria. Cerebrospinal fluid (CSF) is seen as very black areas surrounding the choroid plexus, which is draped around the posterior margins of the thalami.

The infants studied were born to women maintained on methadone and enrolled in the Family Center Program in Philadelphia, a multi-modality program encompassing medical and psychosocial services for pregnant and post-partum drug-dependent women and their children. In addition, a group of infants born to drug-free mothers, of similar medical and socioeconomic status, are included in our evaluation as a comparison group.

An initial group of 24 study infants and 22 controls have been evaluated. Study and control infants were comparable for birth weight, gestational age, apgar scores, sex, race and socioeconomic status. All infants were full-term and healthy, except for abstinence for which 19 of the 24 study infants were treated.

Symptoms of abstinence manifested in our study population included: tremors, increased muscle tone, hyperactive moro reflex, fever, excoriation, nasal stuffiness and high pitched cry. Although mothers of the study infants were on methadone maintenance, with an average daily dose of 44 mg, almost all of the mothers utilized various quantities of heroin, diazepam or amphetamines at least once during their pregnancies. To date, 136 ultrasound studies have been accomplished on the 46 infants, with examinations scheduled for 24 and 72 hours, with followups at 1, 2 and 6 months of age.

Results

In the study and control infants, the ultrasound examinations demonstrated no evidence of hemorrhage or congenital abnormalities of the brain structure and pulsations were normal. The echo-texture of the white matter in the basal ganglia appeared normal in comparison to controls. The interesting finding, in the drug-exposed infants, was the very small size of the lateral ventricles at 24 and 72 hours

of age. Specifically, the finding is lack of visualization of fluid space within the lateral ventricles, or, at most, a very small amount of fluid near the choroid plexus, giving the appearance of slit-like ventricles. Figure 3 shows a parasagittal scan through the lateral ventricles of another study infant. The lateral ventricles, however, are poorly identified due to the lack of fluid within as contrasted to Figure 2 in which the ventricles are clearly identified in a control infant. Figure 4 shows the coronal scanning in the region of the atria in a study infant. The choroid plexes are well seen, but there is no fluid space around them (compared to Figure 1 where a fluid space can be clearly seen).

This occurrence of slit-like ventricles (Table 1) was visualized at 24 hours in seventeen out of nineteen infants prenatally exposed to drugs, whereas only 3 out of 21 control infants had any indication of decreased ventricular size. The pattern follows through for the scans accomplished at 72 hours and 1 month. By 2 months, however, half of the drug-exposed infants studied at that age had ventricles of normal size, and by 6 months of age only 3 out of 11 infants seen still had smaller than normal ventricles. There was no association between these findings and treatment status or dose of methadone. In summary, ultrasound studies have revealed very small to slit-like ventricles in almost all of the passively addicted neonates evaluated, up to one month of age, with resolution to normal size, usually by six months of age.

Table 1

Ventricular configuration of infants born to drug-dependent women vs control infants

Age	Ventricles	Drug-Exposed	Control	
24 hours	Slit-like	17	3	($p < .001$)
	Normal	2	18	
72 hours	Slit-like	20	--	($p < .001$)
	Normal	--	18	
1 month	Slit-like	13	--	($p < .001$)
	Normal	3	11	
2 months	Slit-like	6	*	
	Normal	7**	*	
6 months	Slit-like	3	--	
	Normal	9	6	

*Ultrasound studies were not accomplished at 2 months on controls.
**One of these infants had "normal" size ventricles but exhibited evidence of brain atrophy.

Discussion

Slit-like ventricles may be secondary to diffuse compression of the ventricles bilaterally, as may occur with generalized cerebral edema. However, the pathogenesis remains in question. One might

expect to see some dampening of the arterial pulsations within the cranium if increased intracranial pressure is indeed present. However, there has not yet been any consistent evidence of decreased pulsations. The possibility of edema localized to the periventricular regions cannot be excluded. A localized process adjacent to the ependymal surface, or involving the ependyma, might produce the ultrasound images noted in this study. The peri ventricular brain substance and ependymal lining do not contain pain receptors so that intracranial discomfort is unlikely in the absence of generalized increased pressure. Developmental abnormalities of the ventricular system and ependymal adhesions are not indicated since the size of the lateral ventricles returns to normal generally by six months of age. Decreased cerebrospinal fluid production in the study infants, although a possible cause of slit-like ventricles, should not result in a decreased volume unless bulk absorption of CSF is inexplicably increased or unless CSF production is virtually absent. Thus further studies, including measurements of brain pressure and cerebrospinal fluid production, are indicated. In addition, animal studies could provide information on the pathophysiology of the ventricular findings, particularly related to CSF fluid balance.

It has been reported in many studies (Finnegan, 1978) that symptoms of neonatal abstinence can appear shortly after birth and usually within 2 days after birth in infants born to drug-dependent women. It has also been noted that symptoms, including signs of central nervous system irritability, are frequently manifested for as long as four to six months after birth, even after extended treatment in a hospital setting. In addition to the finding of slit-like ventricles in almost all of the drug-exposed infants, we have been able to obtain an ultrasound scan of a fetal brain (Fig. 5) two weeks prepartally, for one of our subjects. The lateral ventricles appeared to be completely normal. This same study infant manifested slit-like ventricles by 24 hours of age. Therefore, ventricular size seems to correlate with the onset and remission of the neonatal abstinence syndrome. In conclusion, the slit-like ventricles identified in infants born to drug dependent women appear to be a manifestation of the neonatal abstinence syndrome. The present study does not reveal an increased incidence of brain abnormalities in these infants when compared to control infants.

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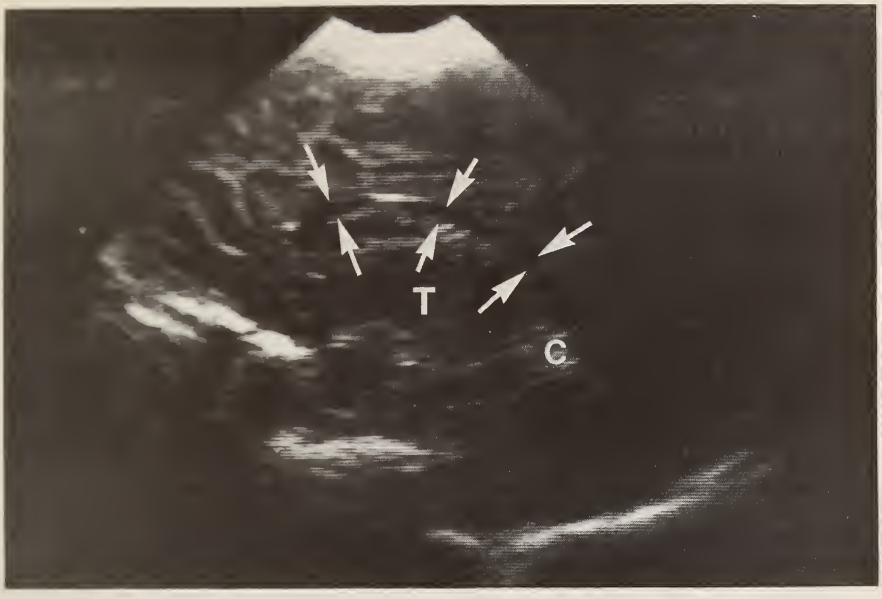

FIGURE 1. This is a parasagittal long axis view of the lateral ventricles in a normal child. The arrows denote the extension of the lateral cerebral ventricle. T represents the thalamus and C represents the choroid plexus.

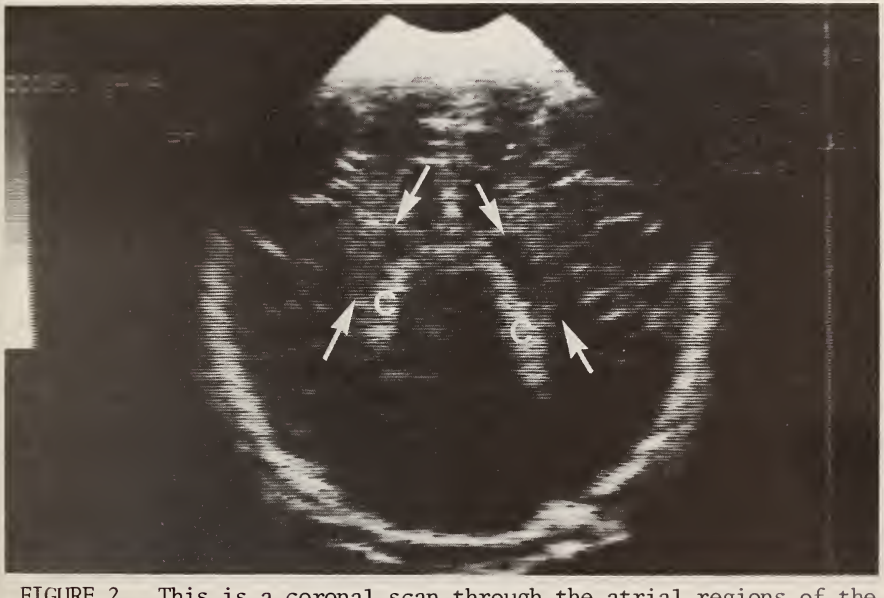

FIGURE 2. This is a coronal scan through the atrial regions of the lateral ventricles in a normal child. The arrows outline the extent of the fluid within the atria of the lateral ventricles. C represents the choroid plexus.

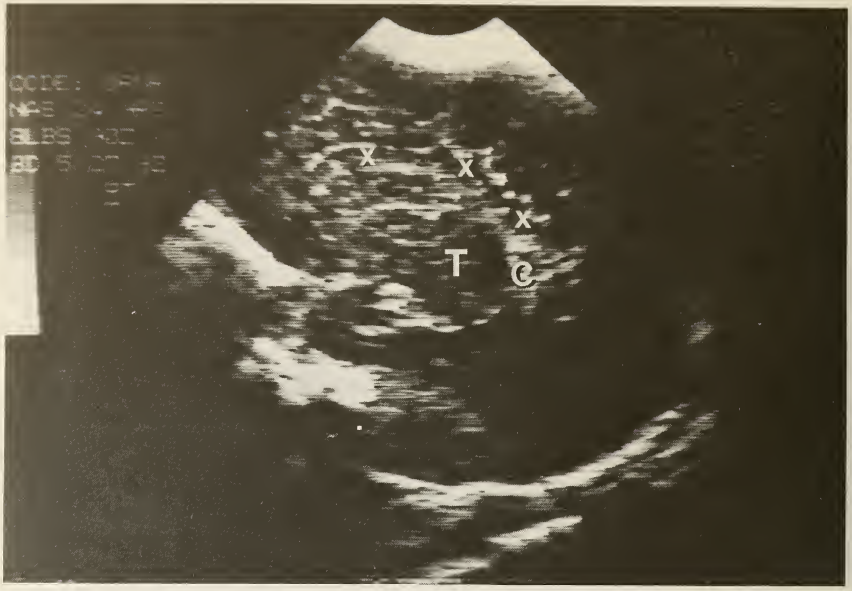

FIGURE 3. Parasagittal scan in a study infant. X's mark the position of the lateral ventricle, which cannot be identified. T represents the thalamus and C represents the choroid plexus.

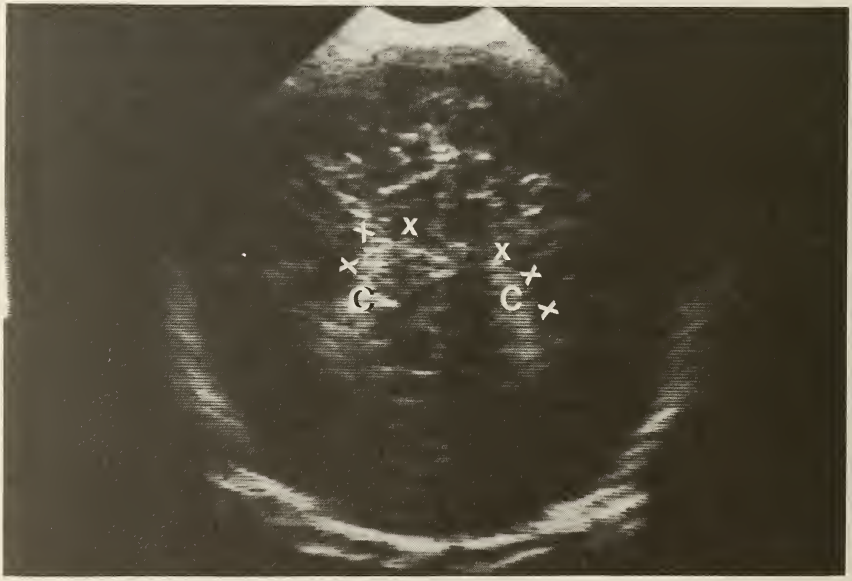

FIGURE 4. This is a coronal scan through the atria of a study infant. X's mark the position of the lateral ventricle, which cannot be identified because of a lack of fluid within it. C represents the choroid plexus.

FIGURE 5. This is a parasagittal scan of a fetal head. B represents the mother's bladder, T represents the thalamus. The arrows outline the lateral cerebral ventricle.

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Nicotine as a Punisher: Effects of Chlordiazepoxide and Mecamylamine on Responding Suppressed by Intravenous Nicotine Injections or by Electric Shocks

Steven R. Goldberg and Roger D. Spealman

ABSTRACT

Squirrel monkeys responded under a two-component fixed-ratio schedule of food presentation with both nonpunishment and punishment components. In both components of the multiple schedule, every 30th key-pressing response resulted in food presentation. In the punishment component, the first response in each 30-response fixed ratio also produced either an i.v. injection of nicotine (10 TO 30 μG/KG) or an electric shock (1 to 5 ma). Response-produced nicotine injections or electric shocks functioned similarly to suppress responding by over 70% in the punishment component. Presession treatment with chlordiazepoxide (5.6 to 10 mg/kg, i.m.) markedly increased responding that had been suppressed by either nicotine injection or electric shock. In contrast, presession treatment with the nicotinic antagonist, mecamylamine (0.1 to 0.3 mg/kg i.m.) increased responding that had been suppressed by nicotine injection but did not increase responding that had been suppressed by electric shock. Thus, chlordiazepoxide appeared to have general rate-increasing effects on suppressed responding, regardless of the nature of the event suppressing responding, while mecamylamine appeared to selectively antagonize the suppressant effects of nicotine. Doses of chlordiazepoxide and mecamylamine that increased suppressed responding in punishment components, generally had little effect on responding in nonpunishment components These results show that under suitable environmental conditions response-produced i.v. injection of nicotine can function effectively as a punisher.

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A Comparison of Bupropion and Amphetamine for Abuse Liability

John D. Griffith, Jose Carranza, C. Griffith, and Loren Miller

ABSTRACT:

Bupropion (±α-tert-meta-chloro-propiophenone; Wellbatrin; Burroughs Wellcome Company), is a substituted phenethylamine which has been shown in clinical trials to be an effective antidepressant. That bupropion might have amphetamine-like abuse potential was suggested by pharmacological studies (drug discrimination in the rat; monkey self-administration) as well as the structural similarity of bupriopion to amphetamine and certain hallucinogenic substances. For this reason, bupropion was examined for abuse potential among 13 healthy informed male inpatient volunteers with histories of psychostimulant abuse. Subjects were given bupropion (100, 200 and 400 mg), d-amphetamine (15 and 30 mg) or placebo at intervals of not less than 4 days according to a double-blind, randomly assigned, crossover design. Drugs were administered orally at 8:00 a.m. Subjects fasted 8 hours before drug administration and 5 hours afterwards.

Bupropion, unlike amphetamine, had no significant effect on supine blood pressure, pulse rate, respiration rate, temperature, appetite, caloric intake or sleep. "Liking" scores for bupropion did not differ from placebo, and bupropion was most often identified as "Blank" (Single Dose Questionnaire). ARCI Subscales (A, BG, MBG, PCAG, LSD) for bupropion resembled those produced by the placebo condition whereas amphetamine was typically amphetamine-like. These findings suggest that bupropion is unlikely to become an amphetamine-like abuse substance.

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The Role of Feedback in the Development of Alcohol Tolerance in Psychomotor Performance

J. V. Hill-Flewelling and M. Vogel-Sprott

Twelve male social drinkers, aged 20 to 25, were trained on the Stressalyser, a complex psychomotor task, until a stable level of performance was attained. Half of the subjects were trained with feedback in the form of knowledge of results; the other half did not receive any information regarding their performance. Subjects receiving feedback attained a stable level of performance more quickly, and became more skilled on the Stressalyser, with respect to speed of performance, than subjects who were not given feedback.

Subjects were then tested on the task under a low dose of alcohol (0.88 ml 94.6 percent alcohol/kg), repeated over four separate sessions. Alcohol impaired performance, but the degree of impairment in the two groups did not differ on any of the drinking sessions, and did not change over sessions.

Although there was no significant development of tolerance (i.e., diminished impairment) over drinking sessions as a function of feedback, half of the subjects in the Feedback group actually displayed less impairment by the final drinking session. This suggests that feedback may have some effect on the development of tolerance to alcohol on this psychomotor task, but it may have been too "weak", or may need to be supplemented with some incentive.

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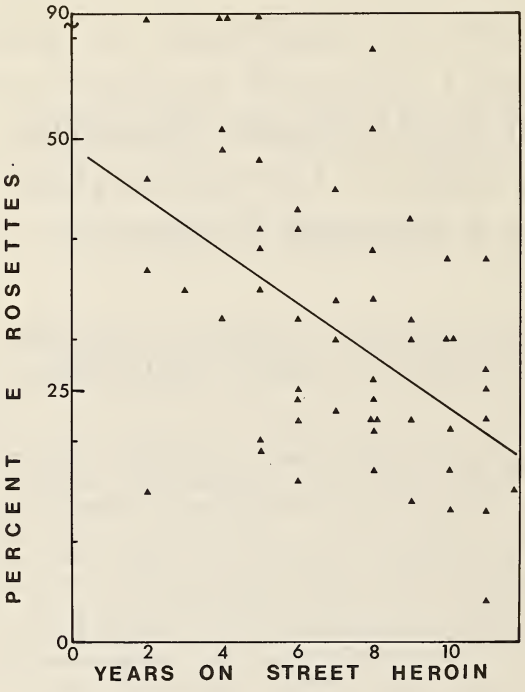
Kinetics of Erythrocyte Rosette Formation With T Lymphocytes From Drug-Addicted Subjects

J. J. Madden, R. M. Donahoe, I. E. Smith, D. C. Eltzroth, F. Hollingsworth, A. Falek, P. J. Bokos, and D. Shafer

Heroin addicts prior to any involvement in methadone therapy (McDonough et al., 1980 & 1981) have a significant decrease in their percent of circulating T lymphocytes as judged by the sheep erythrocyte (E) rosette assay. This E-rosette depression becomes on average more severe the longer the addict uses street opiates (Fig. 1). Addicts in a methadone therapy program (Interventions) generally recover E-rosette capacity within a few months of the start of therapy (Fig. 2)., although a few clients still show a significant T lymphocyte depression after several years of methadone use. These results are consistent with the findings that heroin addiction decreases mitogen-stimulated lymphocyte division. Patterns of mitogen stimulation in lymphocytes from ten methadone clients produced inconsistent results compared to pre-methadone, mitogen-stimulated replication (Brown et al., 1974).

The rates of E-rosette formation by lymphocytes from street opiate addicts, methadone clients, pregnant women who use alcohol, and matched controls for each group were analyzed (Fig. 3 and 4). In controls, the rate of E-rosette formation is best represented by a biphasic curve including a rapid initial rate period of 2-60 minutes in which up to 90% of the rosettes formed, and a slow overnight phase during which rosette formation reached the value reported as total rosettes (Fig. 3). On the other hand, heroin addicts have lower mean percents in both the initial and slow phases of rosette formation. (Fig. 3) However, the kinetic initial rates for addicts and controls were identical after normalization to equalize the differences in the number of lymphocytes with available receptors for sheep erythrocytes present at the start of the assay (Fig. 5). In the case of the methadone clients, the initial rate is briefly slower than control but at 32 min catches up and mimics the control values

Figure 1. Effect of length of street opiate use on % circulating E-rosette forming lymphocytes. E-rosette capacity of 58 opiate addicts was determined as in McDonough et al. (1980). The control matched group had a mean % E-rosette of 72.7 ± 9.6.



thereafter (Fig. 3). From the initial rate measurements, it would appear that one effect of opiate use is a reduction in the number of T lymphocytes and not an alteration of their avidity for sheep erythrocytes.

We also found that lymphocytes from pregnant ethanol users formed rosettes very rapidly, reaching total rosette formation in as little as 10-15 minutes as compared to the hours required by lymphocytes from matched pregnant controls (Fig. 4). In fact, the non-pregnant control group (all ethanol users) and heroin addict group (11 of 13 drank) had initial rates of rosette formation identical to that of the pregnant ethanol users. The methadone group was somewhat slower (only 4 of 10 patients drank), while the non-drinking pregnant controls were slowest of all (Fig 5).

In conclusion, heroin addicts had a reduced percent of T lymphocytes as defined by the capacity to rosette sheep erythrocytes. The avidity of their T lymphocytes for sheep

Figure 2. Effect of methadone therapy on % circulating E-rosette forming lymphocytes. Lymphocytes from 34 methadone clients were tested for E-rosette capacity.

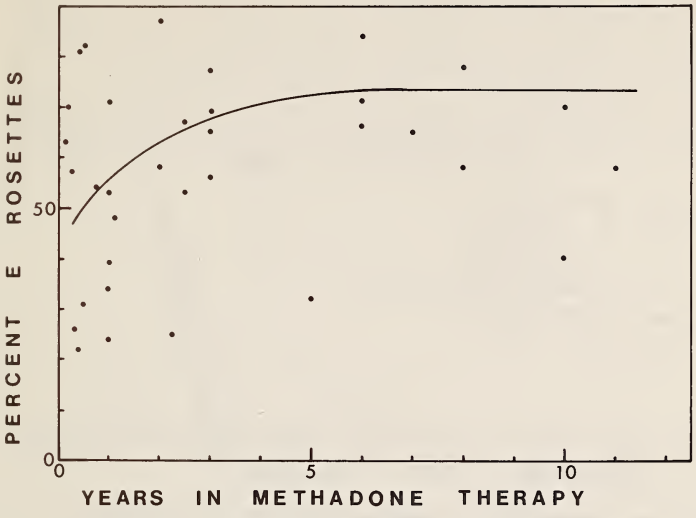


Figure 3. Rate of E-rosette formation by lymphocytes from 13 heroin addicts, 10 methadone clients and 6 matched controls. Lymphocytes and sheep erythrocytes (1:50 ratio) were mixed, incubated at 37°C for 5 min. and centrifuged for 20 sec. at 2000 x g. The rosetting process was stopped by resuspension of the pellet at specific times measured from the start of centrifugation. Rosettes and free lymphocytes were stained with methylene blue and counted at 400 x. Each time point was prepared in triplicate and 100 lymphocytes were evaluated per replicate.

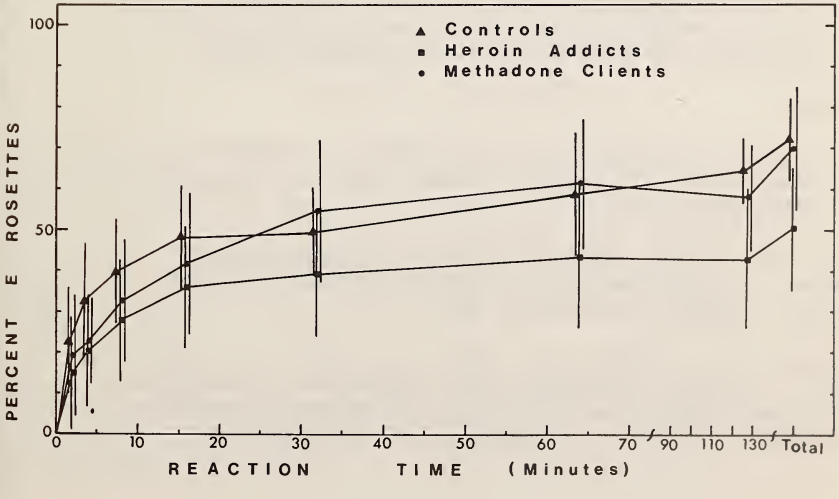
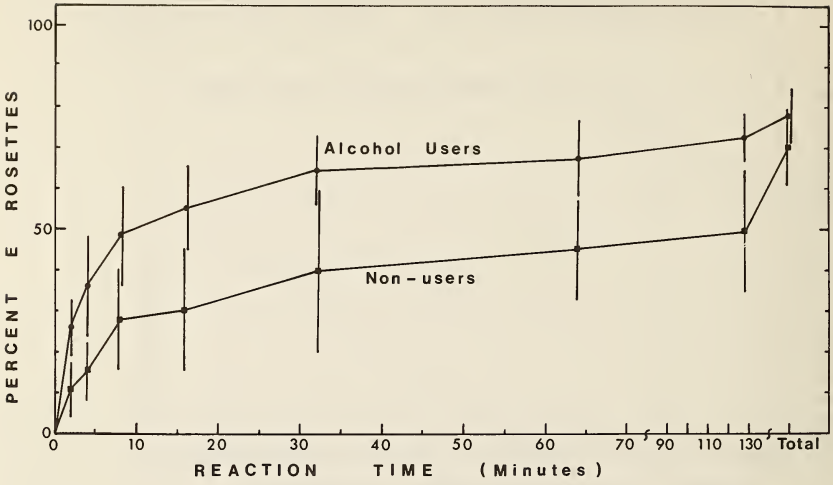


Figure 4. Rate of E-rosette formation by lymphocytes from 11 pregnant women who drink ethanol and 10 matched, pregnant, non-drinking controls.



erythrocytes was comparable to that of control T lymphocytes as judged by kinetic initial rate measurements. This finding suggests that heroin may affect the quantity rather than the quality of the T lymphocytes. Ethanol, on the other hand, appears to increase the initial rate of E-rosette formation in all populations studied, implying a qualitative alteration of the lymphocyte surface. Interestingly, methionine-enkephalin has also been shown to increase formation of "active" rosettes (Wybran et al. 1979). In view of the findings of Hiller et al. (1981), that ethanol inhibits the binding of D-Ala^2-D-Leu^5-enkephalin to the rat brain delta receptor, we speculate that ethanol and enkephalin act at similar sites on the T lymphocyte, increasing lymphocyte rosette capacity.

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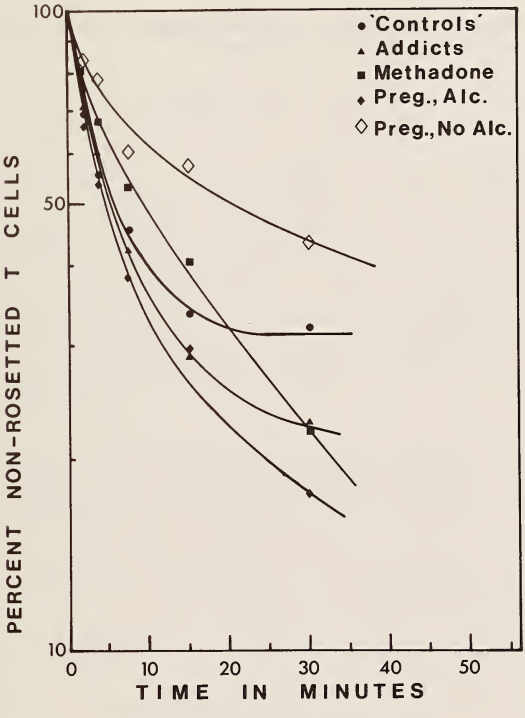
Figure 5. The initial rate of E-rosette formation (as a function of the decrease in free E-rosette postive cells) for controls, heroin addicts, methadone clients, pregnant alcohol users, and pregnant non-drinkers was plotted versus reaction time. The % non-rosetted (free) E-rosette positive cells was calculated from the formula: 100% - (Normalized % E-rosettes). *The* Normalized % E-rosettes *was obtained by normalizing the % E-rosettes for each time point to the overnight value (total) which was set equal to 100%.*



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Analgetic Potentiation by Nalbuphine/Acetaminophen and Nalbuphine/Aspirin Combinations

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ABSTRACT

Oral combinations of nalbuphine with aspirin or acetaminophen demonstrate a significant analgetic potentiation in mice, but only acetaminophen potentiates nalbuphine's narcotic antagonist activity. Using Loewe's isobolographic method, nalbuphine/acetaminophen combinations demonstrate as much as 115% greater than expected analgetic activity in the mouse antiphenylquinone writhing test. The greatest potentiation occurs at 5 min after oral co-administration, corresponding to the analgetic peak-effect times for each drug alone. Less, but still significant potentiation is observed at 10 and 40 min. In contrast, nalbuphine and aspirin demonstrate peak potentiating activity (62-80%) at 20-80 min after oral co-administration, corresponding to the peak effect time of the aspirin component.

Since nalbuphine, acetaminophen, and aspirin share several common metabolic pathways, we hypothesized that a pharmacokinetic/metabolic alteration could explain a portion of the observed potentiation. However, administration of nalbuphine by the s.c. route to avoid its first-pass metabolism reduces its potentiation with acetaminophen (given orally) only slightly. In the mouse anti-Straub tail test, a measure of narcotic antagonist activity where aspirin and acetaminophen are inactive at doses as high as 800 mg/kg p.o., acetaminophen potentiates nalbuphine's oral narcotic antagonist activity up to 2.4X. In support of the pharmacokinetic/metabolic hypothesis, oral acetaminophen does not potentiate s.c. nalbuphine's antagonist activity. A quantitative comparison indicates that a metabolic effect may account for 30% of the observed 115% maximum oral analgetic potentiation, but none of the 90% analgetic potentiation when nalbuphine is administered parenterally. In contrast, aspirin does not potentiate nalbuphine's oral narcotic antagonist activity and oral nalbuphine does not potentiate aspirin's arachidonate lethality protection activity (an *in vivo* measure of aspirin's prostaglandin synthetase inhibitory activity). Thus a pharmacokinetic/metabolic interaction is not likely to be important in the nalbuphine/aspirin analgetic potentiation.

We conclude that pharmacodynamic factors involving independent/covergent analgetic pathways are of a greater importance than pharmacokinetic/metabolic factors in nalbuphine's analgetic potentiation with aspirin and acetaminophen.

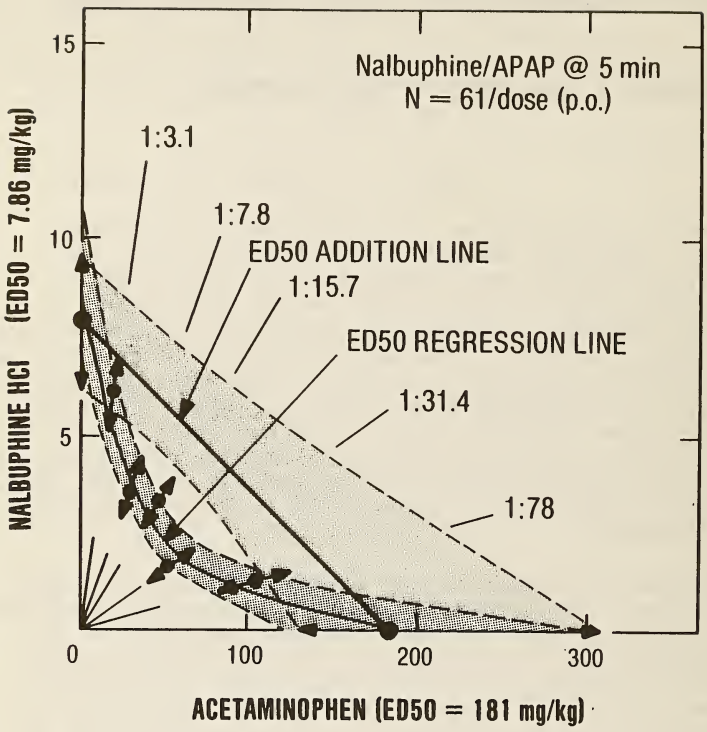

FIG. 1. *Isobologram for the interaction of oral nalbuphine and acetaminophen.* Using Loewe's isobolographic method, oral combinations of nalbuphine and acetaminophen demonstrate analgetic potentiation in the mouse antiphenylquinone writhing (PQW) test. Analgetic potentiation is indicated by a significant difference ($P < 0.05$) between the ED50 Addition Line and the ED50 Regression Line. Data are obtained at 5 min, corresponding to the individual oral analgetic peak effect times for nalbuphine and acetaminophen. Similar data are obtained with s.c. nalbuphine and oral acetaminophen.

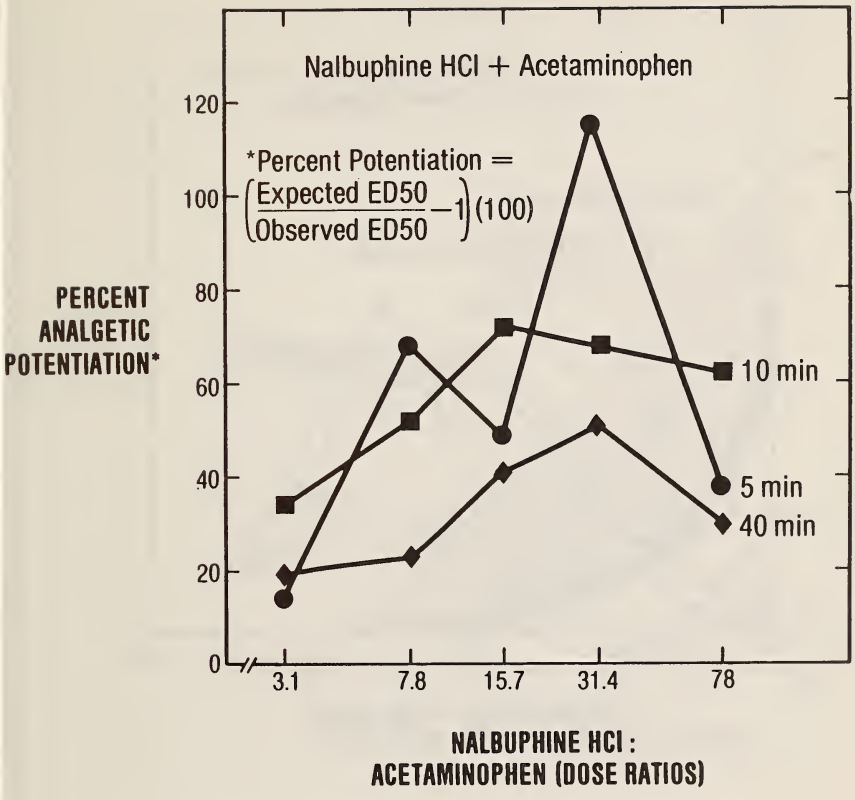

FIG. 2. *Dose ratio/potentiation analysis: nalbuphine and acetaminophen*. Using the data in Fig. 1, oral combinations of nalbuphine and acetaminophen demonstrate as much as 115% analgetic potentiation at 5 min after oral dosing. Significant but lower potentiation is observed at 10 and 40 min.

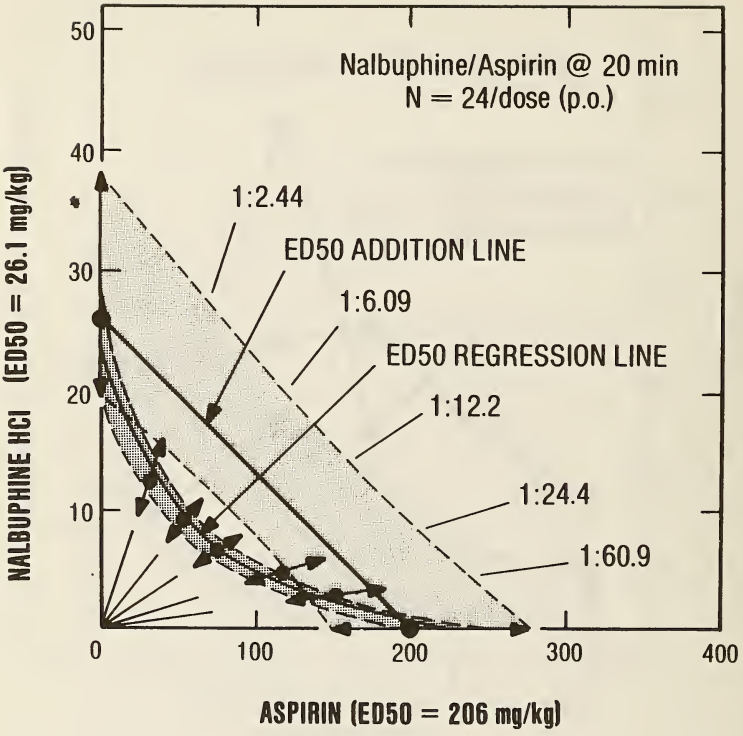

FIG. 3. *Isobologram for the interaction of oral nalbuphine and aspirin.* Oral combinations of nalbuphine and aspirin demonstrate significant ($P < 0.05$) analgetic potentiation in the mouse PQW test. Data are obtained at 20 min, which is intermediate between the individual peak effect times for oral nalbuphine (5 min) and aspirin (40-80 min).

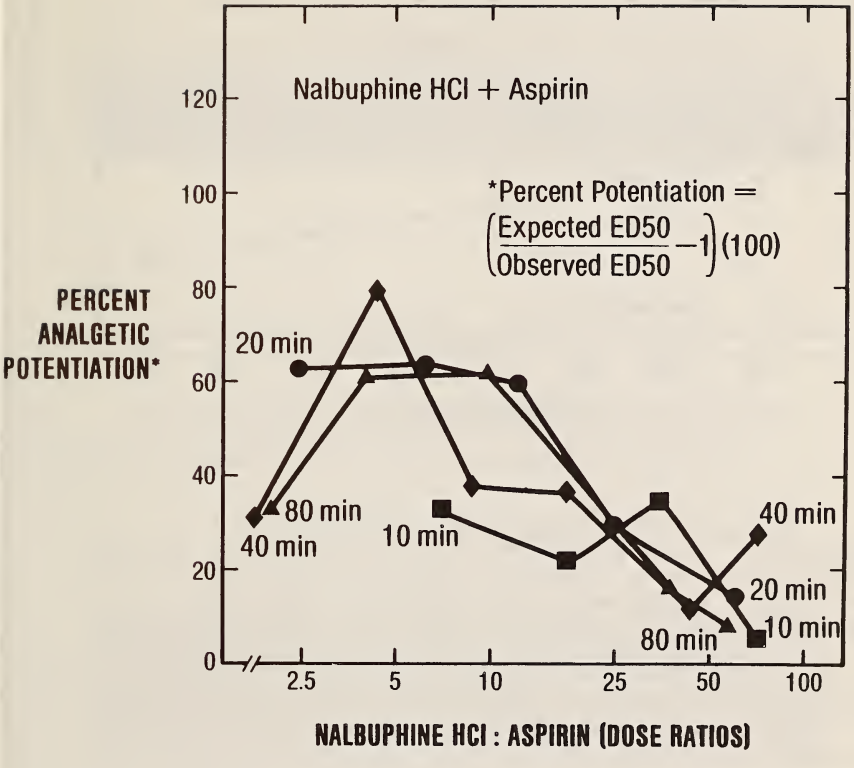

FIG. 4. *Dose ratio/potentiation analysis: nalbuphine and aspirin.* Using the data in Fig. 3, and similar data at other time periods, oral combinations of nalbuphine and aspirin demonstrate as much as 60-80% analgetic potentiation in the mouse PQW test. Peak potentiation is observed at 20-80 min, corresponding to the peak effect time for aspirin alone.

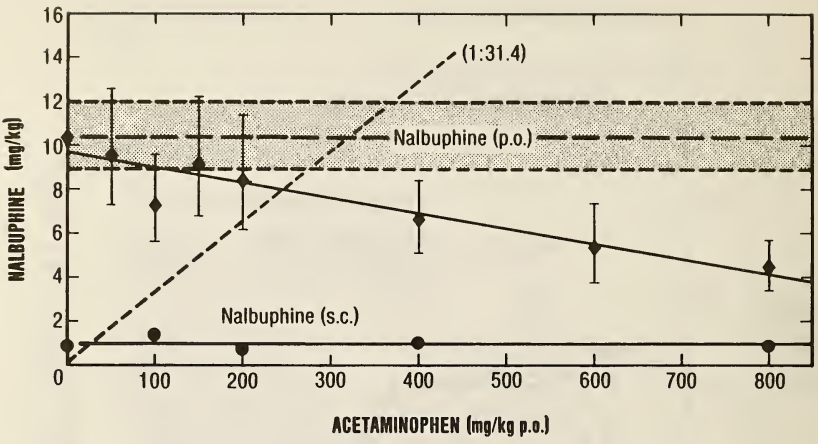

FIG. 5. *Mouse anti-Straub tail test: nalbuphine and acetaminophen.* Co-administration of oral acetaminophen and oral nalbuphine potentiates nalbuphine's narcotic antagonist activity as much as 2.4X in the mouse anti-Straub tail (AST) test. Acetaminophen alone is inactive in this test. However, a 1:31.4 ratio of nalbuphine:acetaminophen produces only 30% narcotic antagonist potentiation, in contrast to the peak 115% analgetic potentiation demonstrated by the same ratio in the mouse PQW test. No antagonist potentiation is observed when nalbuphine is administered s.c.

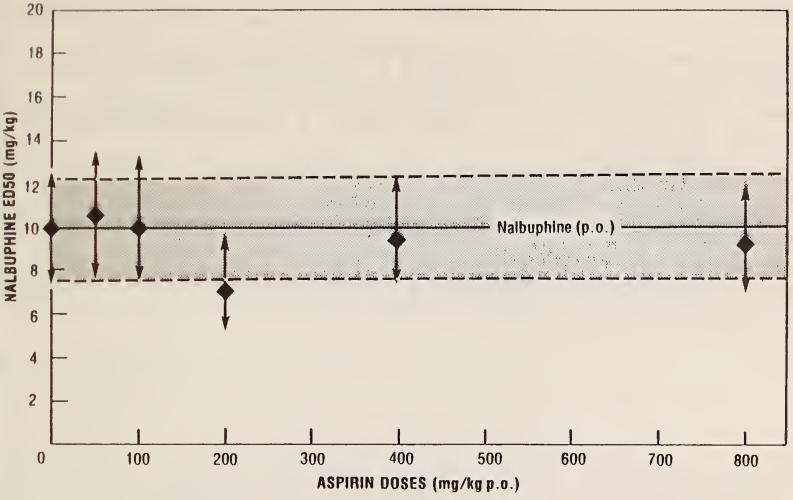

FIG. 6. *Mouse anti-Straub tail test: nalbuphine and aspirin.* In contrast to acetaminophen, similar doses of aspirin do not potentiate nalbuphine's oral narcotic antagonist activity.

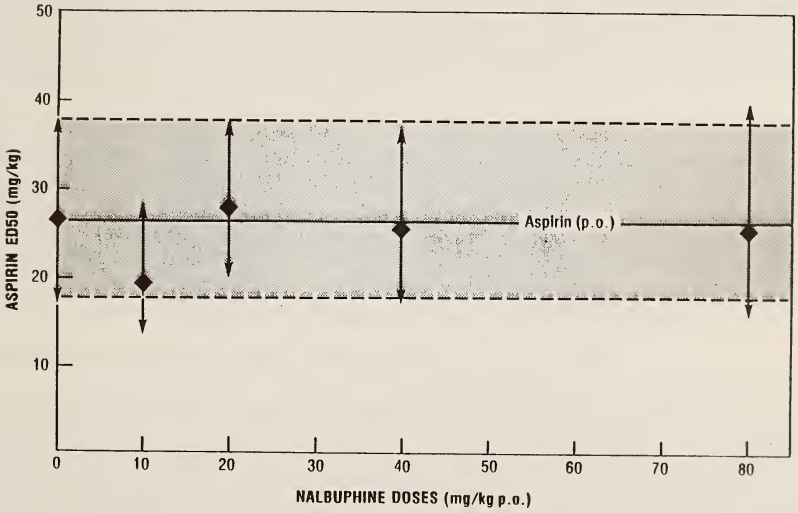

FIG. 7. *Mouse arachidonate lethality protection test: nalbuphine and aspirin.* The arachidonate lethality protection test is an in vivo measure of prostaglandin synthetase inhibitory activity. Mice dosed i.v. with 70 mg/kg sodium arachidonate, pH 8.5, die in respiratroy arrest within 2-5 min in the absence of aspirin or other prostaglandin synthetase inhibitors. Oral nalbuphine does not potentiate aspirin's in vivo prostaglandin synthetase inhibitory activity; nalbuphine alone is inactive.

CONCLUSIONS

Oral combinations of nalbuphine with acetaminophen or aspirin demonstrate a suprising degree of analgetic potentiation in the mouse. The time course for this potentiation is evidently dependent on the peak analgetic effect time of the non-narcotic analgesic in the mixture.

Pharmacodynamic factors involving independent/convergent analgetic pathways are of a greater importance than pharmacokinetic/metabolic factors in nalbuphine's analgetic potentiation with aspirin or acetaminophen, resulting in significantly enhanced analgetic effects without enhanced side effects.

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Biological Evaluation of Compounds for Their Dependence Liability VI. Drug Testing Program of the Committee on Problems of Drug Dependence, Inc. (1982)

A. E. Jacobson

The individual Annual Reports from the Medical College of Virginia (MCV) by Drs. Aceto, Harris and May (Aceto et al. 1982), and from the University of Michigan (UM) by Drs. Woods, Katz, Medzihradsky, Smith, and Winger (Woods et al. 1982) to the Committee on Problems of Drug Dependence (CPDD) are somewhat larger than usual due to the record number of compounds submitted and examined in 1980-1981, and released this year. The Committee is indebted to the groups led by Drs. Harris and Woods for their work which presently represents a considerable part of the utility of the Committee and its public recognition.

The biological testing groups, UM, MCV and NIH, held a few joint meetings last year. One notable meeting was held in the Parklawn Building, where NIDA representatives joined us in considerable number. Dr. Brady's group, from Johns Hopkins, also joined with us on that occasion, and all groups presented an overview of their work. Collaboration between MCV, UM and NIH has, also, resulted in the publication of our first joint paper, on Zomepirac (Woods et al. 1982). Other papers are being scheduled for publication.

COMPOUNDS RECEIVED UNDER THE AUSPICES OF THE CPDD

The same "evaluation year", from May 1 to April 30, was utilized in this report as in my previous reports (Jacobson 1982). In table 1 I have compared data from four years. Thus, it can be seen that the number of compounds sent to MCV/UM ranged between 54 in 1978-1979 and 148 in 1980-1981. The present "evaluation year", 1981-1982, saw about the same number of compounds submitted to our testing groups as in 1979-1980. However, a higher proportion of compounds were submitted in 1981-1982 for examination in tests other than single dose suppression (SDS). About the same number of compounds were submitted for SDS in 1981-1982 as in 1978-1979, down considerably from the number submitted in the intervening two years. The only new record set this year was in the number of reports included in the individual Annual Reports from MCV/UM.

SOURCES OF NEW COMPOUNDS

Comparison of the sources of submitted compounds over the past four "evaluation years" illustrates the inconsistency of these sources. U. S. industry submitted 41% of our samples in 1979-1980, and 8% this year. We can see, in table 1, a considerable reduction in the number of compounds submitted by U. S. industry over the past three years. Spectacularly, foreign industrial sources have reached zero. We will receive at least some of our samples from foreign industries next year, however. The largest number of compounds came from U. S. universities and the National Institutes of Health (NIH). We received 75% of our compounds from the latter two sources in 1981-1982. The number of samples from U. S. universities, on the decline over the past few years, has seen a resurgence this year.

TABLE 1 - DRUG STATISTICS

	5/1/78-4/30/79	5/1/79-4/30/80	5/1/80-4/30/81	5/1/81-4/30/82	MEAN
COMPOUNDS RECEIVED AT NIH (FOR ALL PURPOSES)	124	121	119	137	125
COMPOUNDS SENT TO MCV/UM	28/26=54	51/50=101	67/81=148	43/59=102	101
COMPOUNDS SUBMITTED FOR SDS TO MCV/UM	22/16=38	26/23=49	28/25=53	19/18=37	44
PRIMARY TESTS REQUESTED: MCV/UM[a]	34/26=60	51/57=108	67/82=149	45/63=108	106
PLUS SECONDARY TESTS REQUESTED	56/26=82	77/80=157	95/107=202	64/81=145	147
REPORTS TO CPDD FROM MCV/UM	32/50=82	42/43=85	50/45=~95	75/50=~125	97
SOURCE OF COMPOUNDS (IN %):					
U. S. INDUSTRY	25	41	28	8	26
FOREIGN INDUSTRY	6	22	18	0	12
U. S. UNIVERSITIES	45	30	14	37	32
FOREIGN UNIVERSITIES	6	4	27	15	13
NATIONAL INSTITUTES OF HEALTH	18	1	12	38	17
DRUG ENFORCEMENT ADMINISTRATION	-	1	1	2	-
WORLD HEALTH ORGANIZATION	-	2	-	-	-

a) Compounds could be submitted primarily for in vivo antinociceptive tests alone, in vitro screening alone, or combinations of SDS and other tests. Secondary (further) testing occurred when requested and/or if primary tests were of interest.

TYPES OF COMPOUNDS EXAMINED

In tables 2 through 12 I have compiled the structures of the compounds reported on this year, in a classical medicinal chemistry manner. Thus, there are seventeen epoxymorphinans in tables 2 and 3, twenty morphinans in tables 4 and 5, nine benzomorphans in table 6, ten C-homobenzomorphans in table 7, thirteen phenylmorphans in table 8, five phenylpiperidines in table 9, and five peptides in table 10. Tables 11 and 12 contain fifteen miscellaneous compounds which are not easily classified. All of the compounds which showed antinociceptive activity have at least one aromatic ring and a nitrogen atom. The nitrogen atom can be observed to be either primary, secondary or tertiary in nature, although tertiary amines still predominate. Perhaps one day in the future a better classification scheme will be promulgated based on a compound's primary activity on mu, delta, kappa, or sigma (et al.) opiate receptors, or on a profile based on the ability of specific

antagonists to antagonize the compound's actions in the electrically stimulated guinea pig ileum and mouse vas deferens preparations. The ability of a classical narcotic antagonist, like naltrexone, to antagonize the action of some of these compounds in the guinea pig ileum, but not in the vas deferens, or vice versa, and occasionally the inability of naltrexone to antagonize a compound's action in either preparation is worthy of further study and correlation with other biological parameters (via self-administration and rat infusion studies). It might be worthwhile to examine some of the compounds in man which have interesting profiles from our classical tests and which also show unusual patterns of biochemical behavior in order to try to relate these biochemical differences to analgesia, dependence liability, etc.

It can be noted, in the various tables, that we tested compounds with some unusual structures and compounds with familiar structures which had unusual substituents. As examples of the latter, epoxymorphinans 9651, 9939, 9787, and 9874, in table 2, are structurally classical antagonists which are C-6 fluorinated. Some of them show potent antinociceptive activity in the phenylquinone (PPQ) assay, but not in other antinociceptive assays. The tailflick antagonist assay vs. morphine (TFA) indicates their narcotic antagonist nature, which is corroborated by their precipitation of abstinence in non-withdrawn rhesus monkeys (PW). NIH 9651 is efficacious in the guinea pig ileum (gpi) preparation, but its effect is not antagonized by naltrexone. Others of these fluorinated compounds have little or no effect in the vas deferens (vd) preparation.

Benzomorphan 9807, which has a phenoxypropyl side-chain on nitrogen, did not substitute for morphine in SDS and precipitated withdrawal in non-withdrawn monkeys (table 6). It binds quite well to opiate receptors from rat cerebrum membrane preparations and interacts less well with receptors in the gpi and the vd. The antagonism of its actions by naltrexone in smooth muscle would indicate that it is morphine-like. Indeed, NIH 9807 completely suppressed morphine's action in rat infusion (RI) studies, in agreement with the data from smooth muscle.

The homobenzomorphans, in table 7, generally failed to interact with the opiate receptors from rat cerebrum membrane or smooth muscle preparations. Some had limited antinociceptive activity in the hot plate (HP) and tailflick (TF) assays, but almost all had reasonable activity in the PPQ assay. However, their predominant pharmacological effect in the monkey seemed to be ataxia.

A considerable number of phenylmorphans were examined this year (table 8). Rat infusion studies and smooth muscle data were in agreement about the morphine-like character of NIH 9889. Some of the phenylmorphans were active in the TFA assay and precipitated withdrawal in PW in monkeys.

All of the peptides which were examined (table 10) were essentially morphine-like as antinociceptives, and all completely suppressed withdrawal in SDS. The effects of NIH 9791 on smooth muscle preparations were antagonized by naltrexone, and it was found to be

morphine-like by RI, also. However, that compound, and perhaps other peptides, had reduced reinforcing efficacy in self-injection (SA) studies, as compared with codeine.

Lastly, another extremely potent narcotic was examined at the DEA's request, p-fluorofentanyl (NIH 10022). This compound was, presumably, synthesized in clandestine California laboratories.

Detailed information on all of the compounds listed in these tables is given in the MCV - UM Annual Reports.

ABBREVIATIONS USED IN TABLES

Antinociceptive ED50 values - HP = hot plate assay, sc injection, mice; N = Nilsen assay, sc, mice; PPQ = phenylquinone assay, sc, mice; TF = tail flick assay, sc, mice; TFA = tail-flick antagonism vs. morphine, sc, mice. I = inactive, without a reasonable dose-response relationship, or insufficiently active for statistical analysis; TOX = toxicity precludes assay.

Receptor binding affinities: RBH = binding affinity, without sodium, to rat cerebrum membrane preparations, in nM (parenthesized number is ratio of +Na/-Na) [NOTE: binding affinity of morphine = 60.2 (2.36) except where starred (*). Starred values should be compared with more recent value of binding affinity of morphine = 14.0 (1.69)]. NE = no effect. Smooth muscle preparations: GPI = electrically stimulated guinea pig ileum EC50 values. E = x10; parenthesized numbers are maximum percent inhibition at EC50; bracketed letters: A = antagonized by naltrexone, NA = not antagonized by naltrexone. NE = no inhibition of twitch. VD = electrically stimulated vas deferens EC50 values. Parenthesized numbers and bracketed letters are as listed under GPI.

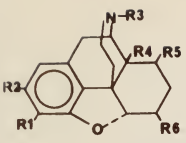
SDS = single dose suppression, rhesus monkeys: NS = no suppression, CS = complete suppression, PS = partial suppression. Parenthesized numbers = dose range studied. Potency comparison with morphine [M] may be stated, in brackets.

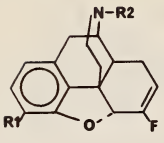
NW = studies in non-withdrawn monkeys: PW = precipitated withdrawal at dose levels indicated in parentheses &/or potency comparison with naloxone [N], in brackets; NE = no effect.

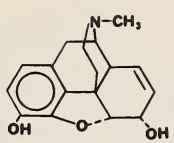
OTHER: RI = rat infusion; NS = no suppression, CS = complete suppression, Little SUBS = little substitution, PS = partial suppression. PPD = primary physical dependence. SA = self-administration; NE = no effect, HIGH = codeine-like.

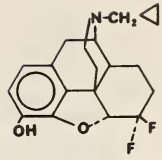
The numbers used in the tables are rounded. For precise values, and details of the procedures, see the Annual Reports of MCV (Aceto et al. 1982) and UM (Woods et al. 1982).

TABLE 2 - EPOXYMORPHINANS[a,b]









9508: R1=OMe,R2=R4=H,R3=CPM,R5=Et,R6=O
9739: R1=R4=OH,R2=NO2,R3=ALLYL,R5=H,R6=O
9874: R1=OAc,R2=R4=R5=H,R3=ALLYL,R6=F,F
9957: R1=R2=R5=H,R3=Me,R4=OH,R6=O
9976: R1=R2=R4=R5=H,R3=ALLYL,R6=O

9787: R1=OAc,R2=CPM
9939: R1=OH,R2=n-Pr

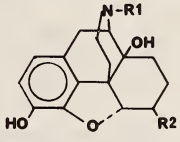
9929 (MORPHINE)
(0001)

9651

NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	RBH	GPI	VD	SDS	NW	OTHER
9508	4142	1325	16.8	I	18.0	I	0.2	-	-	-	NS(3.0-12.0)	PW(6.0-24)	PPD-LOW
9651	4178	1234	17.2	-	0.5	I	0.001	0.5(0.57)	6.1E-9(66)[NA]	1E-4[NA]	NS(0.05-0.2)	PW(0.004-0.25)	
9739	4200	1227	3.5	6.0	3.5	I	3.6	>2uM	-	-	-	-	-
9787	4208	1240	I	I	0.2	I	0.03	3.9(0.58)	-	-	NS(0.25-1.)	PW(0.001)[10xN] LONG DURATION	RI-NS
9874	4230	1322	I	19.8	0.1	I	0.008	4.2(0.5)	3E-9(46)[A]	NE	NS(0.003-0.5)	PW(0.01-0.1)[1xN]	
(9929 0001	4260	1311 0114)	0.87	1.3	0.1	5.0	I	-	-	-	CS(2.5-5.0) CS(3.0-10.0) (0.3-0.5xM)	-	-
9957	-	1338	0.46	-	-	-	-	258*(1.9)	1.1E-6(43)[A]	1.8E-6(100)[A]		-	-
9976	4297	-	6.4	8.3	2.3	I	I	-	-	-	-	-	-
9939	4270	1330	I	I	I	I	0.4	66(0.47)	3.7E-9(57)[A]	1.4E-9(58)[NA]	NS(0.08-1.25)	PW(0.02-1.25)	-

a) See text for explanation of abbreviations.
b) EC50 of morphine=14.0 (1.69), rather than 60.2 (2.36).

TABLE 3 - EPOXYMORPHINANS (CONTINUED)[a,b]



9803: R1=$(CH_2)_2$OMe,R2=O
9930: R1=CPM,R2=O (NALTREXONE)

10001: R1=ALLYL,R2=

10002: R1=ALLYL, R2=NOH

10003: R1=CPM,R2=

10004: R1=CPM,R2=NOH

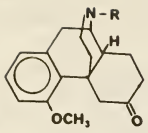
10005: R1=Me,R2=

10008: R1=Me,R2=NOH

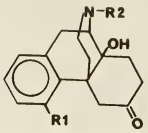
NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	RBH	GPI	VD	SDS	NW
9803	4211	1244	7.7	20.1	0.09	18	I	5.(0.6)	1.5E-9(33)[A]	7.1E-6(37)[A]	NS(0.5)	PW(0.016-0.5)
[9930	4261	1312	I	I	I	I	0.001	I	I	I	NS(0.00015-0.006)	PW(0.0003-0.015[10xN]
8503	4002	0792]									NS(0.1)	PW(0.001-0.03) [10-30xN]
10001	4308	-	I	I	I	I	0.06	-	-	-	-	-
10002	4309	-	I	I	I	I	0.06	-	-	-	-	-
10003	4310	-	I	I	I	I	0.02	0.77*(0.33)	1.1E-7(35)[NA]	4.7E-6(94)[A]	-	-
10004	4311	-	I	I	I	I	0.08	0.9*(0.46)	1.4E-5(97)[NA]	2.9E-5(76)[A]	-	-
10005	4312	-	0.56	0.45	0.1	2.2	I	-	-	-	-	-
10008	4314	-	0.81	2.0	0.05	0.7	I	-	-	-	-	-

a) See text for explanation of abbreviations.
b) EC50 of morphine=14.0 (1.69), rather than 60.2 (2.36).

TABLE 4 - MORPHINANS[a,b]



9926: R=ALLYL
9927: R=Me
9931: R=CPM
9932: R=CH2-

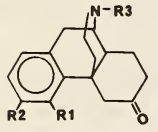


9958: R1=OH,R2=Me
9959: R1=OMe,R2=Me
9975: R1=OH,R2=ALLYL
9977: R1=OMe,R2=CPM
10009: R1=H,R2=Me

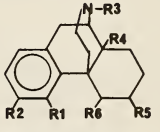
NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	RBH	GPI	VD	SDS	NW
9926	4266 4279	1310	I	-	1.0	4.7	I	-	-	-	NS(1.0-3.0)	PW(0.1-3.0) [0.02xN]
9927	4289	-	1.1	0.4	0.005	0.3	I	-	-	-	CS(0.25-2.0) [10xM]	-
9931	4280	1313	21.7	I	1.2	I	0.4	-	-	-	-	PW(0.1-3.0) [0.03xN]
9932	4281	1314	I	3.6	0.7	I	10.	-	-	-	CS(3.0-10.) [>1xM]	-
9958	-	1339	0.57	-	-	-	-	28*(1.4)	1.9E-7(51)[A]	22E-7(100)[A]	-	-
9959	4305	1340	0.16	-	0.04	3.3	I	71*(1.4)	1.1E-7(55)[A]	2.5E-7(98)[A]	-	-
9975	4296	1347	I	-	8.7	I	3.3	-	-	-	NS(1.0)	PW(0.3-3.0) [0.03xN]
9977	4298	-	I	-	I	I	0.9	-	-	-	-	-
10009	4315	-	0.49	0.53	0.3	0.4	I	340*(1.4)	5.7E-7(82)[A]	2.8E-6(97)[A]	-	-

a) See text for explanation of abbreviations.
b) EC50 of morphine=14.0 (1.69), rather than 60.2 (2.36).

TABLE 5 - MORPHINANS (CONTINUED)[a,b]



9866: R1=OH,R2=OMe,R3=Me
9960: R1=R2=H,R3=Me
9974: R1=OH,R2=H,R3=ALLYL
10010: R1=R2=H,R3=ALLYL
10016: R1=R2=OMe,R3=ALLYL
10017: R1=R2=OMe,R3=CPM
10018: R1=R2=OMe,R3=PHENETHYL

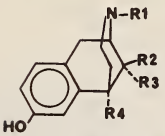


9989: R1=R2=R4=R5=R6=H,R3=Me
10007: R1=R2=R5=R6=H,R3=Me,R4=OH
10011: R1=R2=OMe,R3=Me,R4=OH,R5=O,R6=H
10015: R1=R2=OMe,R3=R6=Me,R4=OH,R5=O

NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	RBH	GPI	VD	SDS
9866	-	1354	2.4	-	-	-	-	239(1.5)	9.6E-8(41)[A]	3.7E-7(100)[A]	-
9960	-	1344	0.33	0.21	-	-	-	90*(1.9)	8.5E-9(70)[A]	1.8E-9(97)[NA]	CS(0.3)[10xM]
9974	4295	-	1.8	-	0.1	0.7	I	-	-	-	-
9989	4299	-	2.3	2.5	2.4	3.9	I	-	-	-	-
10007	4313	-	3.6	4.2	1.0	4.7	I	-	-	-	-
10010	4316		-	2.9	1.8	0.5	6.3	I	-	-	-
10011	-	1380	0.14	-	-	-	-	40(1.2)	4.9E-8(69)[A]	9.7E-7(95)[NA]	-
10015	4317	1381	0.81	-	0.3	2.2	I	105*(1.1)	3.7E-8(64)[A]	9.5E-8(99)[A]	CS(0.3-1.0)[1-3xM]
10016	4318	-	10.6	-	1.5	I	4.6	-	-	-	-
10017	-	1384	3.9	11.1	-	-	-	-	-	-	NE(1-10)
10018	-	1385	0.14	-	-	-	-	-	-	-	CS(3-10)[1xM]

a) See text for explanation of abbreviations.
b) EC50 of morphine=14.0 (1.69), rather than 60.2 (2.36).

TABLE 6 - BENZOMORPHANS[a]

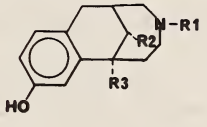


7912: R1=ALLYL,R2=R4=Me,R3=H
9450: R1=R4=Me,R2=$(CH_2)_2CH(CH_3)_2$,R3=H
9454: R1=PHENETHYL,R2=Et,R3=H,R4=Me
9624: R1=R2=R4=Me,R3=$(CH_2)_2CO(CH_2)_4CH_3$
9807: (-)-R1=$(CH_2)_3OC_6H_5$,R2=R4=Me,R3=H
9808: (+)-9807
9809: R1=$CH_2CH(CH_3)OCH_3$,R2=R4=Me,R3=H
9938: R1=$(CH_2)_3CH(CH_3)_2$,R2=R4=Me,R3=H
10024: (-)-R1=$CH_2C{\equiv}CH$,R2=R4=Me,R3=H

NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	RBH	GPI	VD	SDS	NW	OTHER
7912	4267	0902	I	I	2-8	I	0.1	-	-	-	-	-	-
9450	4276	1305	14.1	19.7	13.8	I	I	-	-	-	NS(5.6-17)[b]	PW(~10)[b]	
9454	4288	1146	0.66	-	0.1	6.3	I	-	-	-	-	-	RI-CS(100)
9624	4175	1258	2.4	-	0.2	I	0.03	-	-	-	-	-	RI-LITTLE SUBS(50-200)
9807	4215	1248	0.33	-	0.1	0.8	I	30(3.1)	1.4E-6(68)[A]	6.1E-7(100)[A]	NS(1.2-38)	PW(4-16)	RI-CS
9808	4216	1249	8.7	-	0.5	60	I	NE	NE	NE	NS(6-24)	-	
9809	4217	1250	0.008	-	-	-	-	7.1(2.1)	3.2E-10(61)[A]	2.4E-9(100)[NA]	-	-	
9938	4269	-	8.3	-	2.6	3.3	I	-	-	-	-	-	
10024	4324	-	I	I	0.2	I	0.3	-	-	-	NS(0.02-0.25)	PW(0.13-0.5)[0.04xN]	

a) See text for explanation of abbreviations.
b) Preconvulsive.

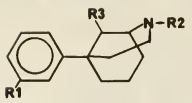
TABLE 7 - C-HOMOBENZOMORPHANS



9614: R1=R3=Me,R2=H
9895: (+)-R1=ALLYL,R2=H,R3=Me
9896: (-)-9895
9897: (±)-9895
9899: (+)-R1=CPM,R2=H,R3=Me
9900: (-)-9899
9903: (+)-R1=$CH_2CH{=}C(Me)_2$,R2=H,R3=Me
9904: (-)-9903
9905: (±)-9903
9906: (±)-R1=$CH_2CH{=}C(Me)_2$,R2=R3=Me

NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	RBH	GPI	VD	SDS	NW
9614	4169	1269	2.5	13.0	0.5	I	6-13	3760(1.3)	2E-6(82)[NA]	NE	NS	PW(3-12)
RI(SDS) - NS; RI(PPD) - OPIATE-LIKE; PPD-DEPENDENCE-PRODUCING; SA-MINIMAL												
9895	4235	1290	I	I	0.6	I	I	NE	7.4E-7(42)[A] SIMILAR TO CLONIDINE, BACLOFEN	1.8E-7(70)[NA]	NS(0.025-2)	
9896	4236	1291	I	I	4	I	7	NE	NE	NE	NS(0.13-2)	NE(0.25-4)
9897	4248	1279	I	I	0.4	I	1.1	6010(1.6)	NE	1E-6(30)[NA]	NS(0.1-1) PCP-LIKE	-
9899	4237	1292	I	I	5	2	I	NE	1.1E-5(40)[NA]	NE	PS(0.01-1)	NE(0.25-1)
9900	4238	1293	I	I	0.2	I	I	NE	NE	NE	NS(1.25-10)	NE(0.3-5)
9903	4254	1315	10.1	-	1.8	I	I	NE	4.6E-6(49)[A]	1.5E-6(70)[A]	NS(1-10)	-
9904	4252	1278	I	I	17.3	I	I	NE	NE	NE	NS(5.6)[SLIGHT WITHDR.(10)]	
9905	4264	1308	I	-	6.9	I	I	NE	NE	NE	NS(1-10)	NE(CONVULSIONS)
9906	4265	1309	11.5	-	2.1	12	I	364(1.7)	2.2E-6(63[NA]	NE	PS(5.6)	-

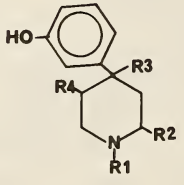
TABLE 8 - PHENYLMORPHANS



9881: (-)-R1=OH,R2=R3=H
9882: (-)-R1=OH,R2=Me,R3=H
9883: (-)-R1=OH,R2=Et,R3=H
9887: (-)-R1=OH,R2=n-HEXYL,R3=H
9888: (+)-R1=OH,R2=R3=H
9889: (+)-R1=OH,R2=Me,R3=H
9890: (+)-R1=OH,R2=Et,R3=H
9891: (+)-R1=OH,R2=n-PROPYL,R3=H
9945: R1=OMe,R2=R3=CH_3
9955: R1=OH,R2=R3=Me
9971: (-)-R1=OH,R2=Me,R3=β-Me
9972: (+)-9971
10021: R1=R3=OAc,R2=Me

NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	RBH	GPI	VD	SDS	NW	OTHER
9881	4239	1282	I	-	I	I	I	3360(0.5)	9.5E-9(15)[A]	NE	-	-	-
9882 8508	4240	1283	2.0	-	1.3	5.5	I	487(0.9)	4.5E-9(31)[A]	1.3E-6(63)[NA]	-	-	RI-PS
9883	-	1284	TOX.	I	-	-	-	3650(0.5)	1.5E-7(44)[A]	NE	-	-	-
9887	4234	-	TOX	I	20.2	I	2.1	-	-	-	NS(0.08-1.25)	PW(0.08-1.25)	-
9888	4243	-	I	-	I	I	I	-	-	-	-	-	-
9889 8509	4244	1288	0.63	-	0.2	0.8	I	57(1.5)	1.8E-7(95)[A]	9.9E-7(100)[A]	-	-	RI-CS
9890	4245	1289	15.8	-	28	I	I	1462(1.1)	1.9E-5(92)[NA]	1.1E-6(49)[NA]	-	-	-
9891	4246	1275	9.2	-	2.5	I	I	1970(0.9)	2.2E-5(90)[A]	NE	NS(1.0-5.6)	-	-
9945	4286	1327	I	-	I	I	I	-	-	-	NS(5-30)	NE(17)	-
9955	4275	-	9.3	-	I	I	5.0	-	-	-	NS(0.25-4)	PW(4)	-
9971	4293	-	I	I	1.9	I	I	-	-	-	NS(2.5-10)	PW(2.5-10)	-
9972	4294	-	I	I	I	I	4.5	-	-	-	NS(4,8)	PW(3-12)	-
10021	-	1388	2.0	-	-	-	-	-	-	-	NS(1-10)	-	-

TABLE 9 - 4-PHENYLPIPERIDINES



9769: R1=$(CH_2)_5OCOCH_3$,R2=R4=H,R3=COEt
9771: R1=Me,R2=R4=H,R3=CH(OH)Et
9790: R1=$(CH_2)_2CH(CH_3)C_2H_5$,R2=R4=H,R3=COEt
9806: R1=$(CH_2)_2C(C_6H_5)_2CON(Me)_2$,R2=R4=H,R3=COEt
9922: R1=R2=R3=R4=Me

NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	RBH	GPI	VD	SDS
9769	-	1232	23.6	-	-	-	-	2200(0.9)	2.3E-6(44)[A]	NE	NS(5-20)
9771	4205	1236	I	-	I	I	I	-	3.4E-6(92)[A]	7.5E-7(83)[A]	NS(2.5-20)
9790	4209	1241	16.6	-	12.9	I	I	515(1)	-	-	NS(2.5-10)
9806	4214	1247	20.5	-	-	-	-	86(1.1)	1.2E-7(54)[A]	4.3E-8(91)[A]	NS(3-10)
9922	4259	-	2.4	-	0.5	2.9	I	-	-	-	CS(1.5-6)

TABLE 10 - PEPTIDES

9791 - N-Me-L-Tyr-D-SerGly-N-Me-L-PheAla-D-Serinaminde

9947 - L-Tyr-D-AlaGly-L-4-F-PheAla-L-Phenylglycinamide

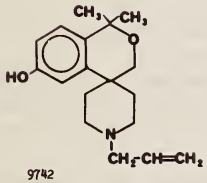
9948 - L-Tyr-D-AlaGly-N-α-Et-L-m-Br-Phenylalanine amide

9949 - N-α-Me-L-Tyr-D-AlaGly-N-α-Et-L-p-F-Phenylalanine amide

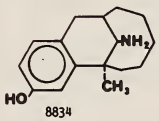
9950 - N-α-Me-L-Tyr-D-AlaGly-N-α-Cyclopropylmethyl-L-m-Br-Phenylalanine amide

NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	RBH	GPI	VD	SDS
9791	4210	1238	1.4	1.5	0.1	3.5	I	133(1.9)	6.1E-8(56)[A]	7.2E-8(97)[A]	PS(32),CS(64)
RI - OPIATE-LIKE; SA-REDUCED REINFORCING EFFICACY.											
9947	4271	-	2.1	-	0.06	15.4		I	-	-	CS(8)
9948	4272	-	3.3	-	0.5	11.3		I	-	-	CS(8)
9949	4273	-	0.7	-	0.06	2.5	I	-	-	-	CS(3)
9950	4274	-	2.1	-	0.02	11.8	-	I	-	-	CS(2.5-10)

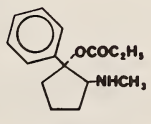
TABLE 11 - MISCELLANEOUS



9742

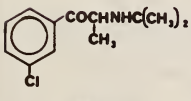


8834

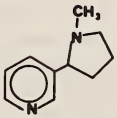


9721

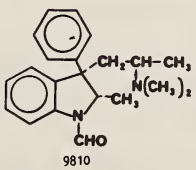
VIMINOL
8893



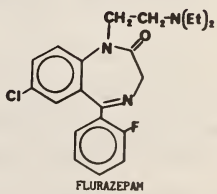
BUPROPION
9788



(+)-NICOTINE
9801



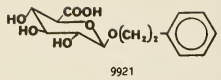
9810



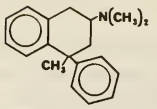
FLURAZEPAM
9827

NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	RBH	GPI	VD	SDS	NW	OTHER
8834	4206	0972	0.7	0.9	0.3	2.6	I	-	-	-	NS(1.25-5)-EXACERBATES WITHDR.		
RI(PPD)-LESS THAN MORPHINE; SA - BETWEEN CODEINE AND SALINE.													
8893	4224	1009	1.2	0.7	2.7	12.8		I	-	-	NS(SC ADMIN.)(6-36) CS(IV ADMIN.)(0.5-2)		
9721	4186	1216	I	0	25.5	147	I	I	I	I	NS(1.25-5)	NE(2.5-40)	SA-NE
9742	-	1222	I	-	-	-	-	NE	NE	NE	-	-	-
9788	-	1239	I	25.8	-	-	-	-	-	-	-	-	SA-HIGH
9801	4235	-	23.2	38.2	I	I	I	-	-	-	PS(0.5-4)	-	-
9810	4218	1251	I	28.9	15.4	I	I	NE	6.7E-7(93)[NA]	NE	NS(5-20)	-	-
9827	4223	1256	I	-	15.7	I	I	NE	1.6E-5(94)[NA]	1.7E-9(60)[NA]	PS(15)	-	-

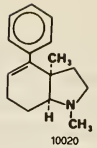
TABLE 12 - MISCELLANEOUS (CONTINUED)



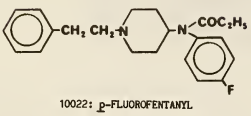
9921



9940: (±)-trans
9941: (-)-trans
9942: (+)-trans
9943: (-)-cis



10020



10022: p-FLUOROFENTANYL

NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	RBH	GPI	VD	SDS	NW
9921	4253	-	I	-	NE	NE	NE	-	-	-	-	-
9940	4282	-	I	-	4.4	I	I	-	-	-	-	-
9941	4283	-	13.1	-	3.0	I	I	-	-	-	-	-
9942	4284	-	I	-	2.3	I	I	-	-	-	-	-
9943	4285	-	5.6	-	1.9	I	I	-	-	-	-	-
10020	4322	-	I	-	I	I	1.7	-	-	-	NS(1-4)	PW(4,8)
10022	4323	-	0.02	-	0.006	0.03	I	-	-	-	CS(0.01,0.04)	-

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Dependence Studies of New Compounds in the Rhesus Monkey, Rat, and Mouse (1982)

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All the test drugs were supplied by Dr. Arthur Jacobson, Medicinal Chemistry Section, NIADDK under the auspices of the Committee on Problems of Drug Dependence, Inc. The chemical structures of the test compounds excluding SKF 10,047 and (+)-Nicotine were unknown to us when they were originally submitted.

For the most part, the procedures described by Seevers and his colleagues (1936, 1963) and Deneau (1956) regarding the facilities and training of the monkeys were used and a brief description follows. The monkeys were injected with 3 mg/kg/sc of morphine sulfate every 6 hours for at least 90 days before being used. This dose schedule was reported by Seevers and Deneau (1963) to produce maximal physical dependence.

Modified procedures for the precipitated withdrawal (PPt-W) and single dose suppression (SDS) tests were reported by Aceto and co-workers (1977 and 1978). The PPt-W test was initiated by the

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injection of a test drug 2½ hours after an injection of morphine, and the animals were observed for signs of withdrawal. The SDS test was started approximately 15 hours after the last dose of morphine at which time the animals were showing withdrawal signs. The onset and duration of action of the test drug were noted. In both tests, a vehicle control and an appropriate postive control [naloxone 0.05 mg/kg or morphine sulfate 3.0 (mg/kg)] along with 3 different treatments (doses) of a test compound were randomly allocated to the 5 monkeys of a group. Occasionally 4 monkeys comprised a group and 2 doses of test compound were studied. Usually, 3 or 4 groups per compound were used. All drugs were given subcutaneously or intravenously (1 ml/kg) and the vehicle used is indicated for each compound. The observer was "blind" with regard to the treatment given. A minimum 2-week washout and recuperation period between tests was allowed. In the primary physical dependence (PPD) test, the animals of a group received the drug every 4-6 hours for 30-50 days. They were placed in abrupt withdrawal and challenged with naloxone periodically, and were observed for signs of physical dependence. All potency estimates are rough approximations only.

The rat-infusion method was reported by Teiger (1974) and certain modifications are indicated below. Semi-restrained male, Sprague-Dawley rats were medicated by continuous infusion through indwelling, intraperitoneal cannula for 6 days with the drugs. Rats were anesthetized and each was fitted with a specially prepared cannula which was passed subcutaneously from the nape of the neck to the lateral side of the lower abdomen and then inserted in the peritoneal cavity. The cannula was anchored at both ends with silk sutures and attached to a flow-through; swivel mechanism which allowed the animal to move about in the cage and eat and drink normally. The swivel was connected to a syringe which was attached to a syringe pump. The animals received 7 to 10 ml of solution every 24 hours.

In the substitution for morphine (SM) test, the rats first received morphine (50 mg/kg/24 hrs on the first day, 100 mg/kg/24 hr on the second day, and 200 mg/kg/24 hr from days 3-6). Then, a test drug was substituted for 2 days. The morphine controls received an infusion of water. The animals were observed for changes in body weight and for behavioral-withdrawal signs for ½ hour at 6,24,48,72 and/or 96 hours after stopping the infusion of morphine.

In the primary physical dependence (PPD) study, the rats received test compound for 6 days and then were placed in abrupt withdrawal and observed as above.

Table 1

Comparative Data-ED50 mg/kg/sc (95% C.L.) of Selected Standards in 3 Mouse Agonist-Antagonist Tests

Drug	Tail Flick Test	Tail-Flick Antagonism Test	Phenylquinone Test
Pentazocine	15% at 10.0	18 (12.4-26)	1.65 (1.0-2.5)
Cyclazocine	17% at 1.0[a]	0.03 (0.02-.78)	0.011 (0.0046-0.03)
Nalorphine .HCL	None at 10.0	2.6 (0.69-9.75)	0.6 (0.25-1.44)
Naloxone .HCL	None at 10.0	0.035 (0.010-0.093)	No Activity
Naltrexone .HCL	None at 10.0	0.007 (0.002-0.02)	No Activity
Morphine Sulfate	5.8 (5.7-5.9)	-----	0.23 (0.20-0.25)

[a]Mice were ataxic at 3.0 and 10.0 mg/kg but no further increase in reaction time was seen.

Three mouse tests were used in our laboratory at the Medical College of Virginia to provide a preliminary estimate of the potency and profile of activity of each test compound. The tests were the tail-flick agonist (TF) and the morphine antagonist (TF vs M) tests and the phenylquinone (PPQ) test (Dewey et al., 1970; Dewey and Harris, 1971). Reference-standard data for these tests are shown in table 1. In addition, Dr. Jacobson provided us with estimated starting doses. These doses were based on results obtained from the mouse hot plate (HP) (Eddy and Leimbach, 1953; Jacobson and May, 1965; Atwell and Jacobson, 1978) and Nilsen (N) (Perrine et al., 1972) tests from his laboratory. Reference data for these tests are shown in table 2.

Table 2

Comparative Data (ED50 mg/kg/sc) [95% S.E.] from the Hot Plate and Nilsen Test

Compound	Hot Plate Test Subcutaneous Oral	Nilsen Test Subcutaneous Oral
Morphine Sulfate	0.98(0.83-1.1) 6.3(4.7-8.3)	1.3(1.0-1.7) 8.3(6.0-11.4)
Codeine Phosphate	6.8(4.5-10.2) 13.5(9.7-18.7)	7.4(4.9-11.0) 14.7(9.2-23.3)
Levorphanol Tartrate	0.2(0.1-0.3) -	0.2(0.16-0.3) 2.5(1.7-3.7)
Meperidine .HCL	5.3(4.0-7.1) -	- -
(-)-Metazocine .HBr	0.6(0.5-0.9) 10.6(8.0-14.1)	0.5(0.3-0.7) 26.0(21.0-33.0)
Dihydromorphinone .HCL	0.19(0.15-0.25) 0.9(0.7-1.2)	0.2(0.15-0.3) 1.8(1.5-2.1)
Nalorphine .HCL	9.9(5.7-17.1) -	23.0(16.2-32.7) -
Cyclazocine	1.5(1.1-2.1) -	0.1(0.07-0.16) -
Pentazocine	9.3(6.7-12.8) -	6.5(4.4-8.8) -
Chlorpromazine .HCL	1.1(0.9-1.5) -	- -

Naloxone .HCL and Naltrexone HCL No dose-response

Phenobarbital, Amobarbital, Valium, Oxazepam, Flurazepam, Meprobamate and Mescaline are inactive on the hot plate test.

SUMMARY OF COMPOUNDS TESTED[a]

COMPOUND #			CHEMICAL CLASS	MOUSE					RAT		MONKEY		
MCV	NIH	UM		TF,	TFvsM,	PPQ,	HP,	N	SM,	PPD	SDS	PPt-W	PPD
4142	9508	1325	Dihydrocodeinone	+	+	+	+	+					+
4169	9614	1269	C-Homobenzomorphan	+	+	+	+	+	+			+	+
4175	9624	1258	6,7-Benzomorphan	+	+	+	+		+				
4178	9651	1234	3-Hydroxymorphinan	+	+	+	+				+	+	
4186	9721	1216	1-Phenylcyclopentanol	+	+	+	+					+	
4200	9739	1227	14-Hydroxymorphinone	+	+	+	+	+					
4206	8834	927	Benzocyclodecenol	+	+	+	+	+				+	
4209	9790	1241	Ketobimidone (4-Phenylpiperidine)	+	+	+	+				+		
4211	9803	1244	14-Hydroxymorphinone	+	+	+	+	+					
4214	9806	1247	Ketobemidone (4-Phenylpiperidine)	+	+	+	+						
4215	9807	1248	6,7-Benzomorphan	+	+	+	+		+		+	+	
4216	9808	1249	6,7-Benzomorphan	+	+	+	+	+			+		
4224	8893	1009	Benzylprrole	+	+	+	+	+					

SUMMARY OF COMPOUNDS TESTED

COMPOUND #			CHEMICAL CLASS	MOUSE					RAT	MONKEY		
MCV	NIH	UM		TF,	TFvsM,	PPQ,	HP,	N	SM, PPD	SDS	PPt-W	PPD
4230	9874	1322	3-Aetoxymorphinan	+	+	+	+	+			+	
4231	9882	809	Phenylmorphan	+	+	+	+		+			
4232	8509	810	Phenylmorphan	+	+	+	+		+			
4234	9887	-	Phenylmorphan	+	+	+	+			+	+	
4236	9896	1291	1H-4-Benzazonine	+	+	+	+	+			+	
4237	9899	1292	1H-4-Benzazonine	+	+	+	+			+	+	
4238	9900	1293	1H-4-Benzazonine	+	+	+	+	+			+	
4239	9881	1282	Phenylmorphan	+	+	+	+					
4240	9882	1283	See MCV 4231									
4243	9888	-	Phenylmorphan	+	+	+	+					
4244	9889	1288	Phenylmorphan	+	+	+	+					
4245	9890	1289	Phenylmorphan	+	+	+	+					
4246	9891	1275	Phenylmorphan	+	+	+	+					
4248	9897	1279	1H-4-Benzazonine	+	+	+	+					

SUMMARY OF COMPOUNDS TESTED

COMPOUND #			CHEMICAL CLASS	MOUSE				RAT		MONKEY		
MCV	NIH	UM		TF,	TFvsM,	PPQ,	HP,	N	SM, PPD	SDS	PPt-W	PPD
4252	9904	1278	1H-4-Benzazonine (C-Homobenzomorphan)	+	+	+	+					
4253	9921	-	Uronic acid glycoside	+	+	+	+					
4254	9903	1315	1H-4-Benzazonine (C-Homobenzomorphan)	+	+	+	+			+		
4259	9922	-	4-Phenylpiperidine	+	+	+	+			+		
4260	9929	1311	Morphine	+	+	+	+	+		+		
4261	9930	1312	14-Hydroxymorphinone (Naltrexone)	+	+	+	+			+	+	
4264	9905	1308	1H-4-Benzazonine (C-Homobenzomorphan)	+	+	+	+					
4265	9906	1309	1H-4-Benzazonine (C-Homobenzomorphan)	+	+	+	+					
4266	9926	1310	Morphinan-6-one	+	+	+	+					
4267	4912	902	6,7-Benzomorphan	+	+	+	+	+				
4269	9938	-	6,7-Benzomorphan	+	+	+	+					

SUMMARY OF COMPOUNDS TESTED

COMPOUND #			CHEMICAL CLASS	MOUSE					RAT	MONKEY		
MCV	NIH	UM		TF,	TFvsM,	PPQ,	HP,	N	SM, PPD	SDS	PPt-W	PPD
4270	9939	1330	3-Hydroxymorphinan	+	+	+	+			+	+	
4271	9947	-	Pentapeptide	+	+	+	+			+		
4272	9948	-	Pentapeptide	+	+	+	+			+		
4273	9949	-	Pentapeptide	+	+	+	+			+		
4274	9950	-	Pentapeptide	+	+	+	+			+		
4275	9955	-	Phenylmorphan	+	+	+	+			+	+	
4276	9450	1305	6,7-Benzomorphan	+	+	+	+	+				
4279	9926	1310	See MCV 4266									
4280	9931	1313	Morphinan-6-one	+	+	+	+	+				
4281	9932	1314	Morphinan-6-one	+	+	+	+	+				
4282	9940	-	Tetrahydronaphthylamine	+	+	+	+					
4283	9941	-	Tetrahydronaphthylamine	+	+	+	+					
4284	9942	-	Tetrahydronaphthylamine	+	+	+	+					
4285	9943	-	Tetrahydronaphthylamine	+	+	+	+					

SUMMARY OF COMPOUNDS TESTED

COMPOUND #			CHEMICAL CLASS	MOUSE					RAT	MONKEY		
MCV	NIH	UM		TF,	TFvsM,	PPQ,	HP,	N	SM, PPD	SDS	PPt-W	PPD
4286	9945	1327	Phenylmorphan	+	+	+	+					
4288	9454	1146	6,7-Benzomorphan	+	+	+	+		+			
4289	9927	-	Morphinan-6-one	+	+	+	+	+		+		
4293	9971	-	Phenylmorphan	+	+	+	+	+		+	+	
4294	9972	-	Phenylmorphan	+	+	+	+	+		+	+	
4295	9974	-	Morphinan-6-one	+	+	+	+					
4296	9975	1347	Morphinan-6-one	+	+	+	+					
4297	9976	-	Epoxymorphinan-6-one	+	+	+	+	+				
4298	9977	-	14-Hydroxymorphinan-6-one	+	+	+	+	+				
4299	9989	-	Morphinan	+	+	+	+	+				
4305	9959	1340	14-Hydroxymorphinan-6-one	+	+	+	+					
4308	10,001	-	14-Hydroxymorphinone	+	+	+	+	+				
4309	10,002	-	14-Hydroxymorphinone	+	+	+	+	+				
4310	10,003	-	14-Hydroxymorphinone	+	+	+	+	+				

SUMMARY OF COMPOUNDS TESTED

COMPOUND #			CHEMICAL CLASS	MOUSE					RAT	MONKEY		
MCV	NIH	UM		TF,	TFvsM,	PPQ,	HP,	N	SDS, PPD	SDS	PPt-W	PPD
4311	10,004	-	14-Hydroxymorphinone	+	+	+	+	+				
4312	10,005	-	14-Hydroxymorphinone	+	+	+	+	+				
4313	10,007	-	14-Hydroxymorphinone	+	+	+	+	+				
4314	10,008	-	14-Hydroxymorphinone	+	+	+	+	+				
4315	10,009	-	14-Hydroxymorphinone-6-one	+	+	+	+	+				
4316	10,010	-	Morphinan-6-one	+	+	+	+	+				
4317	10,015		Morphinan-6-one	+	+	+	+					
4318	10,016	-	Morphinan-6-one	+	+	+	+					
4322	10,020	-	Hydroxyphenyl-1H-indole	+	+	+	+			+	+	
4323	10,022	-	4-Anilinopiperidine (Fentanyl)	+	+	+	+			+		
4324	10,024	-	6,7-Benzomorphan	+	+	+	+	+		+	+	
4325	9801	-	Pyrindylpyrrolidine (+)-(Nicotine)	+	+	+	+	+		+		

A "+" indicates compound tested as shown.

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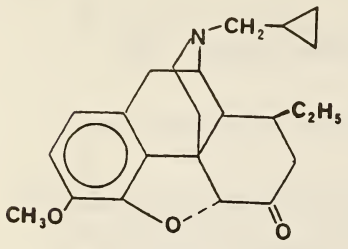
MCV 4142, NIH 9508, UM 1325. N-Cyclopropylemthyl-8β-ethyl-N-nordihydrocodeinone hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - Inactive at 1.0, 3.0 and 30.0

2) TF vs M - 0.2 (0.03 - 1.5)

3) PPQ - 18.0 (7.5 - 43.6)

4) HP - 16.8 (10.5 - 26.9)

5) N - no dose-responses, 4/8 at 50.0 and 100.0

MONKEY DATA (PPD)

Five drug naive rhesus monkeys were given MCV 4142 dissolved in H_2O every 6 hr. The animals were observed for 15 min, approximately one half hour after receiving drug.

Day	Dose mg/kg/sc	Comments
1	2.0	During the first 2 days, the only drug-induced behavioral effect noted was wet-dog shakes. By day 3, some showed drowsiness and by the end of day 4, all were drowsy. Some salivation occurred on day 5 and all were drowsy. Wet-dog shakes seemed not to occur as often when drowsiness was present. On day 6, wet-dog shakes was the main effect noted. After the last injection on day 8, one animal convulsed and the other appeared to be in a preconvulsive state; salivation and tremors were also seen in all the animals. After the dose was reduced and from days 9 - 14, the principal signs noted were: drowsiness, wet-dog shakes, salivation and jaw sag.
2	4.0	
3	6.0	
4	9.0	
5	12.0	
6	15.0	
7	18.0	
8	21.0	
9	18.0	
10	19.0	
11	20.0	
12	21.0	
13-14	19.0	
15		PPT-Withdrawal - After a challenge dose of 1.0 mg/kg of naloxone, the principal withdrawal signs noted were: lying on side or abdomen, fighting, avoiding contact, restlessness, wet-dog shakes, yawning and retching. The onset was prompt and the effects lasted less than 90 minutes.

15	20.0	Resumed study at noon. Restlessness, drowsiness,
16-17	19.0	wet-dog shakes, jaw sag and salivation were the
18-21	20.0	main drug effects seen. Two of the animals de-
22-23	21.0	veloped skin ulcers. It was noted that these
24	22.0	animals positioned themseleves so that they were
25-28	23.0	being injected in the same area. From that time
29	24.0	onward, the animals were held and the site of in-
		jection was rotated. The ulcers healed without
		incident.
30	25.0	Abrupt Withdrawal. Virtually no signs were seen
		12-15 hours after the last dose.

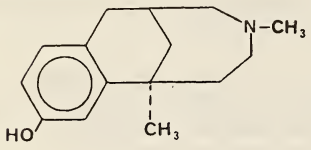
PPT-Withdrawal - A 2.0-mg/kg dose of naloxone at 16 hours elicited the following signs. Lying on side or abdomen, fighting, pacing, drowsiness, wet-dog shakes, retching, coughing, yawning and vocalizing when abdomen palpated.

30	25.0	MCV 4142 injections were resumed at noon.
		Drowsiness, tremors, wet-dog shakes, salivation
		and jaw sag were noted. One monkey had convul-
		sions. The dose was reduced to 20.0 mg/kg.
31	21.0	During the period 31-44 days the principal drug
32-34	22.0	effects noted were drowsiness, wet-dog shakes,
35	23.0	salivation and jaw sag. On day 39, one monkey
36	24.0	developed convulsions.
37	25.0	
38	26.0	
39	27.0	
40-44	27.0	
45		Abrupt Withdrawal. During the observation period of 12-18 hr, the only withdrawal signs noted were avoiding contact, restlessness, and wet-dog shakes.

PPt-Withdrawal. A. 2.0-mg/kg dose of naloxone elicited the following signs: lying on side or abdomen, fighting, avoiding contact, yawning restlessness, drowsiness, retching, and vocalizing when abdomen palpated.

Conclusion. In the dose schedule tested, MCV 4142 produced few withdrawal sign during abrupt withdrawal. A withdrwal syndrome was precipitated by a high dose of naloxone. Convulsions may have limited the degree of physical dependence. All the animals but one gained weight throughout the study.

MCV 4169, NIH 9614, UM 1269. (-)-9-Hydroxy-4,7-dimethyl-C-homobenzomorphan hydrobromide.



MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

1) TF - a. Inactive at 3.0, 6.0, 10.0 and 30.0

b. Inactive at 3.0, 10.0 and 30.0

2) TF vs M - a. 13.4 (5.7 - 31.3)

b. 5.5 (1.2 - 25.9)

3) PPQ - a. 0.5 (0.2 - 1.7)

b. 0.4 (0.1 - 1.3)

4) HP - a. 1.8 (1.3 - 2.4)

b. 2.5 (1.9 - 3.3)

5) N - 13.0 (9.6 - 17.7)

MONKEY DATA (PPt-W) # ANIMALS Doses (mg/kg/sc) 3, 3, 3 / 12.0, 6.0, 3.0
Vehicle - H_2O

Certain signs designated as lying on side or abdomen, drowsiness, ataxia, restlessness and tremors were seen. However, only one animal retched, one salivated and two vocalized when the abdomen was palpated. This drug appeared to have very weak antagonist and/or strong depressant properties.

MONKEY DATA (PPD) # ANIMALS Doses (mg/kg/sc)

A group of 5 monkeys which had not received any drug for at least 3 months was given MCV 4169 as indicated below and observed for behavioral signs for approximately 15 min ½ hr after drug was administered or as indicated below. The drug was dissolved in H_2O and the volume given was ¼ - 1.0 ml/kg.

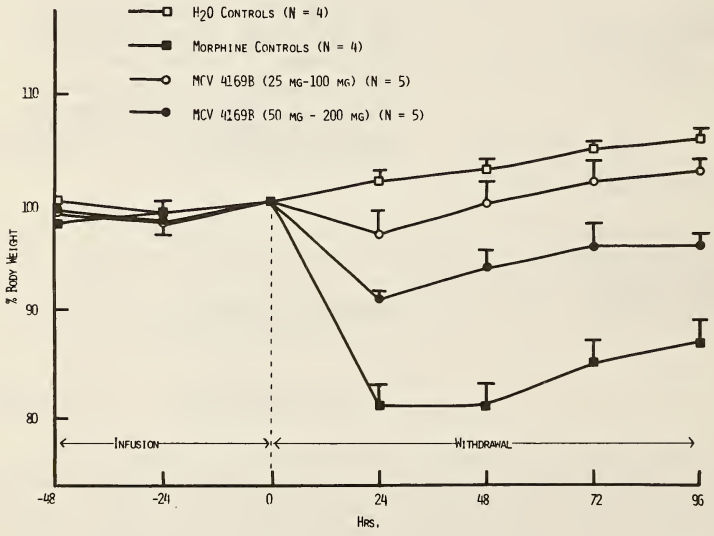
Day	Dose mg/kg/sc (Times/Day)	Comments
1	1.0 (4x8)	The principal signs noted were vocalization, ataxia (at times severe). Drowsiness and slowing were also seen on occasion.
2	2.0 (4xd)	
3	4.0 (4xd)	
4	6.0 (4xd)	

Day	Dose mg/kg/sc (Times/Day)	Comments
5-8	8.0 (4xd)	Few signs were seen at the 2 lower doses.
9	9.0 (4xd) and 4.5 (2xd)	
10	9.0 (6xd)	
11	9.0 (5xd) and 4.5 (1xd)	
12	9.0 (4xd) and 4.5 (2xd)	
13-14	9.0 (4xd)	The following withdrawal signs were noted: 5/5 rigid abdomen, 3/5 fighting, restless drowsy fighting, retching, and vocalized when abdomens palpated; 2/5 avoids contact, wet-dog shakes; 1/5 vocalizing and, coughing.
15 at 8:30 AM	PPT-W Naloxone 2.0 mg/kg	
15 Resumed study at noon	9.0 (4xd) and 4.5 (1xd)	
16	9.0 (5xd) and 4.5 (1xa)	
17-21	9.0 (6xd)	
22-25	10.0 (6xd)	
26-28	11.0 (6xd)	
29-30	12.0 (5xd)	
31 at 8:35 AM	PPT-W Naloxone 0.5 mg/kg	During precipitated withdrawal the following signs were seen: 5/5 drowsy; 4/5 restless 3/5 rigid abdominal muscles and retching; 2/5 vocalized when abdomens palpated; 1/5 wet dogs.
31 at noon	12.0 (5xd)	
33-36	12.0 (6xd)	
37-38	13.0 (6xd)	
39-40	14.0 (6xd)	
41-44	15.0 (6xd)	(Cont'd next page)

45 Abrupt Withdrawal. The abrupt withdrawal syndrome peaked 10-12 hour after the last injection and was recorded as follows: 5/5 rigid abdomen; 4/5 vocalized when abdomens palpated; 2/5 lying on side; 1/5 fighting, avoids contact, vocalized and masturbation. By 18 hours no obvious signs were noted.

Conclusions. The drug definitely produced signs of opiate-like physical dependence. Tolerance also developed to its effects. All the animals lost body weight but by the end of the study 3/5 had either regained or exceeded the original starting weights. The physical dependence liability is judged to be intermediate to high.

Rat Infusion (PPD): According to the data shown in the figure and table, MCV 4169 produces an opiate-type primary physical dependence in the rat. The results are dose-related regarding weight loss and behavioral withdrawal signs.



Table

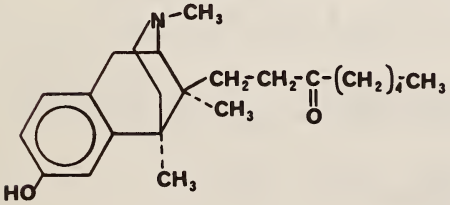
Mean Number of Withdrawal Signs[1] Noted During a 1/2 Hr Observation Period at Specified Intervals and Calculated Probability Values[2] for Comparisons Between H_2O Only Group and MCV 4169 and Morphine Control.

	Hr in withdrawal				
	6	24	48	72	96
H_2O Controls N=4	x = 0	x = 1.8	x = 1.3	x = 0.5	x = 1.5
Morphine Infusion H_2O Substitution N=4	x = 4.3 p = 0.01	x = 14.8 p = 0.01	x = 18.5 p = 0.01	x = 21.0 p = 0.02	x = 13.3 p = 0.05
MCV 4169 Infusion 50, 100, 200x4 mg/kg N=5	x = 3.2 p = 0.05	x = 6.6 p = 0.45	x = 9.2 p = 0.05	x = 12.0 p = 0.05	x = 10.0 p = 0.14
MCV 4169 25, 50, 100x4 mg/kg H_2O Substitution	x = 4.2 p = 0.05	x = 0.8 p = 0.36	x = 1.4 p = 0.45	x = 3.0 p = 0.05	x = 2.2 p = 0.36

1) Hypersensitivity, squealing, aggression, wet dog shakes, rubbing and chewing.

2) One-tailed test (Mann Whitney U-Test).

MCV 4175, NIH 9624, UM 1258. 1-[2α,6α,11S)-(±)-1-(1,2,3,4,5,6-Hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocin-11-yl)]-3-octanone methanesulfonate.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - Inactive at 1.0, 10.0 and 30.0

2) TF vs M - 0.03 (0.01 - 0.7)

3) PPQ - 0.2 (0.08 - 0.6)

4) HP - 2.4 (1.7 - 3.3)

RAT INFUSION (PPD)

When given at doses comparable to those administered to the morphine controls, little weight loss (Fig.) and few withdrawal signs (Tables 1 and 2) were noted. An unexpected but non-significant spurt in the number of withdrawal signs did occur 96 hours after MCV 4175 was abruptly withdrawn. Whether or not this was a spurious event or may represent delayed emerging withdrawal cannot be ascertained from this study. Additional studies are recommended if indicated.

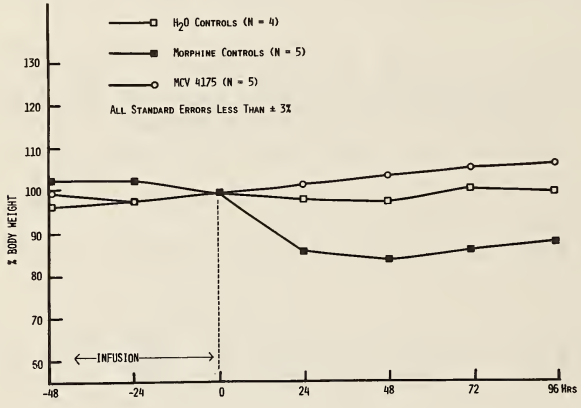


Table 1

Mean Number of Withdrawal Signs[1] Noted During a 1/2 Hr Observation Period at Specified Intervals and Calculated Probability Values[2] for Comparisons Between MCV 4175 and Morphine Control.

	Hr in Withdrawal			
	24	48	72	96
Morphine Controls N = 5	x = 13.4	x = 19.2	x = 16.0	x = 14.0
MCV 4175 Infusion (50 mg/kg-day 1, 100 mg/kg-day 2, 200 mg/kg-days (3-6) N=5	x = 2.8 p = 0.008	x = 1.4 p = 0.004	x = 4.8 p = 0.016	x = 10.6 p = 0.274

1) Hypersensitivity, squealing, aggression, wet dog shakes, rubbing and chewing.

2) One-tailed test (Mann Whitney U-Test).

Table 2

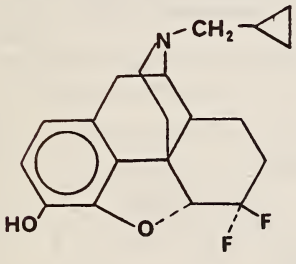
Mean Number of Withdrawal Signs[1] Noted During a 1/2 Hr Observation Period as Specified Intervals and Calculated Probability Values[2] for Comparisons Between H_2O Only Group and MCV 4175.

	Hr in Withdrawal			
	24	48	72	96
H_2O Controls N = 4	x = 1.5	x = 4.8	x = 3.0	x = 4.0
MCV 4175 Infusion (50 mg/kg-day 1, 100 mg/kg-day 2, 200 mg/kg - days 3-6), N = 5	x = 2.8 p = 0.452	x = 1.4 p = 0.056	x = 4.8 p = 0.143	x = 10.6 p = 0.278

1) Hypersensitivity, squealing, aggression, wet dog shakes, rubbing and chewing.

2) One-tailed test (Mann Whitney U-Test).

MCV 4178, NIH 9651, UM 1234. 17-Cyclopropylmethyl-4,5α-epoxy-6,6-difluoro-3-hydroxymorphinan hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - Inactive at 3.0, 10.0 or 30.0

2) TF vs M - 0.001 (0.003 - 0.005)

3) PPQ - 0.5 (0.05 - 4.3)

4) HP - 17.2 (7.3 - 40.4)

MONKEY DATA A) (SDS) # ANIMALS Doses (mg/kg/sc) 2, 2, 2, 0.2, 0.1, 0.05 Vehicle - H_2O

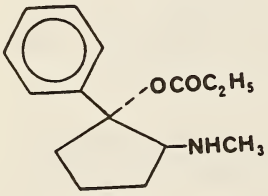
In the dose range tested, MCV 4178 did not substitute for morphine.

MONKEY DATA B) (PPT-W) # ANIMALS Doses (mg/kg/sc) 1, 1, 0.25, 0.125, 2, 2, 1, 2, 1, 1, 0.062, 0.031, 0.015, 0.008, 0.004, 0.002 Vehicle - H_2O

MCV 4178, NIH 9651, UM 1234 (Cont'd)

MCV 4178 was active at all doses but the lowest in precipitating withdrawal signs. The drug acted promptly and the duration of action is longer than that of naloxone. Approximately 10 x as potent as naloxone.

MCV 4186, NIH 9721, UM 1216. 2β-Methylamino-1-phenylcyclo-pentanol propanoate ester, hydrogen maleate.



MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

1) TF - 0% at 1.0, 18% at 10.0, and 22% at 30.0

2) TF vs M - a) Inactive at 1.0, 10.0, 50.0, and 100.0, b) 0% at 1.0 and 30.0

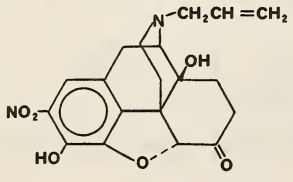
3) PPQ - 25.0 (14.8 - 43.9)

4) HP - Incompletely active at 100.0

MONKEY DATA (PPt-Withdrawal)	# ANIMALS Doses (mg/kg/sc)	1 / 40.0, 2 / 20.0, 3 / 10.0, 2 / 5.0, 1 / 2.5
		Vehicle - H_2O

In the dose range studies, MCV 4186 did not precipitate withdrawal signs in morphine-dependent monkeys.

MCV 4200, NIH 9739, UM 1227. 2-Nitronaloxone



MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

1) TF - 0% at 1.0, 17% at 10.0 5/6 died at 30.0

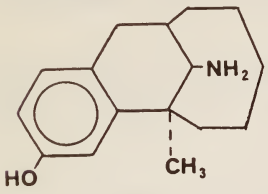
2) TF vs M - 3.6 (0.8 - 16.8)

3) PPQ - 3.5 (1.8 - 6.8)

4) HP - 3.5 (2.8 - 4.3)

5) N - 6.0 (4.5 - 8.0)

MCV 4206, NIH 8834, UM 972. (-)-13β-Amino-5,6,7,8,9,10,11,12-octahydro-5α-methyl-5,11-methanobenzocyclodecen-3-ol hydrobromide.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - 2.6 (0.8 - 8.1)

2) TF vs M - 16% at 1.0, 18% at 10.0 and 6% at 30.0

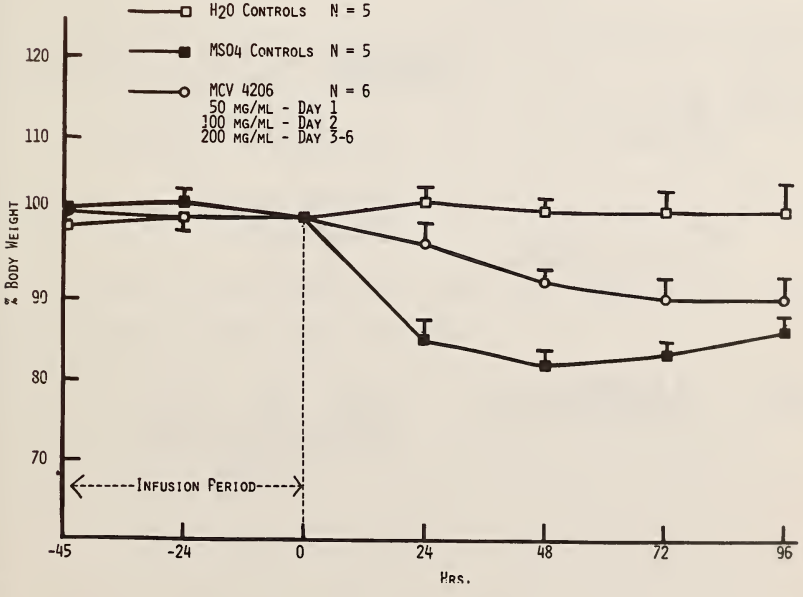
3) PPQ - 0.3 (0.07 - 1.0)

4) HP - 0.7 (0.5 - 0.9)

5) N - 0.9 (0.7 - 1.1)

RAT INFUSION (PPD)

MCV 4206 given chronically produces weight loss when abruptly withdrawn (See Fig.). The weight loss is not as precipitous during the first 24 hr as is that shown by the morphine-infused controls. Furthermore, the animals were still losing weight at 96 hours whereas the morphine controls appeared to be regaining weight. The same pattern was noted regarding withdrawal signs. A significant difference was not noted until the 72-hr observation period (see table). The withdrawal reaction seems to be delayed. The drug appears to produce physical dependence in rats although the degree of dependence may not be as intense as that shown for morphine.



Table

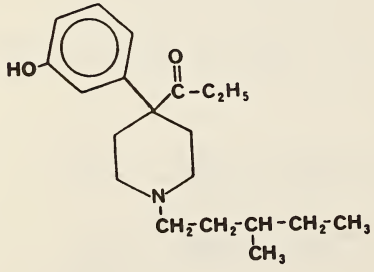
Mean Number of Withdrawal Signs[1] Noted During 1/2 Hr Observation Period at Specified Intervals and Calculated Probability Values[2] for Comparisons Between H_2O Only Group and MCV 4206 and Morphine Control.

	Hr in Withdrawal			
	24	48	72	96
H_2O only N = 5	x = 2.0	x = 1.0	x = 0.4	x = 1.2
Morphine Controls N = 5	x = 10.4 p = 0.004	x = 11.0 p = 0.008	x = 13.8 p = 0.004	x = 10.2 p = 0.004
MCV 4206 Infusion (50 mg/kg-day 1, 100 mg/kg-day 2, 200 mg/kg-days 3-6). N = 6	x = 3.0 p = 0.535	x = 5.5 p = 0.106	x = 8.2 p = 0.007	x = 6.0 p = 0.089

1) Hypersensitivity, squealing, aggression, wet dog shakes, rubbing and chewing.

2) One-tailed test (Mann Whitney U-Test).

MCV 4209, NIH 9790, UM 1241. 3-Methylpentyl-N-norketobemidone hydrobromide.



MOUSE DATA-ED_{50} (955 C.L.) (mg/kg/sc)

1) TF - 4% at 11.0 and 13% at 30.0

2) TF vs M - 0% at 1.0 and 27% at 30.0

3) PPQ - 12.9 (3.0 - 55.7)

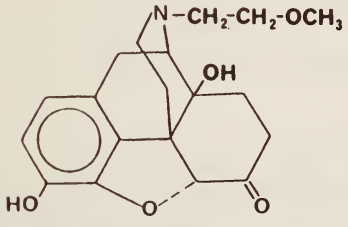
4) HP - 16.6 (12.5 - 22.1)

MONKEY DATA (SDS)	# ANIMALS Doses (mg/kg/sc)
	2, 2, 2 10.0, 5.0, 2.5 Vehicle-Lactic Acid and H_2O

MCV 4209, NIH 9790, UM 1241 (Cont'd)

The drug did not substitute for morphine. It may have exacerbated withdrawal. Severe tremors were noted in two monkeys. Drug supply was exhausted.

MCV 4211, NIH 9803, UM 1244. (-)-N-(2-Methoxyethyl)noroxymorphone hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - 17.9 (13.8 - 23.2)

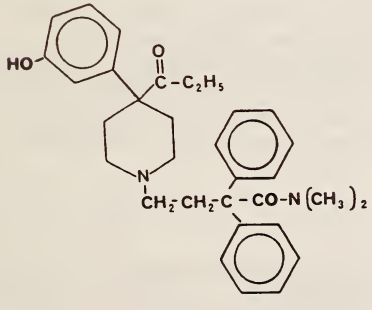
2) TF vs M - 10% at 1.0 and 30.0

3) PPQ - 0.09 (0.01 - 0.95)

4) HP - 7.7 (5.9 - 10.0)

5) N - 20.1 (15.9 - 25.4)

MCV 4214, NIH 9806, UM 1247. N-[3-(N,N-Dimethylcarbamoyl)-3,3-diphenylpropyl]-norketobemidone hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

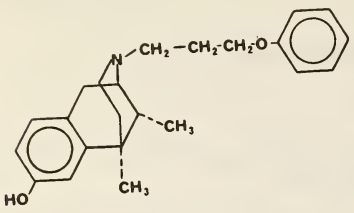
1) TF - Inactive at 1.0 and 30.0

2) TF vs M - Inactive at 1.0, 10.0 and 30.0

3) PPQ - 1% at 1.0, 33% at 10.0, 36% at 30.0, 72% at 60.0

4) HP - 20.5 (13.6 - 30.9)

MCV 4215, NIH 9807, UM 1248. (-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(3-phenoxypropyl)-6,7-benzomorphan hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

1) TF - 0.8 (0.2 - 2.6)

2) TF vs M - Inactive at 1.0 and 30.0

3) PPQ - 0.1 (0.06 - 0.4)

4) HP - 0.3 (0.2 - 0.4)

MONKEY DATA	# ANIMALS					
A) (SDS)	Doses (mg/kg/sc)	1	2	3	2	3
		38.4	19.2	19.6	2.4	1.2
		Vehicle - H_2O				

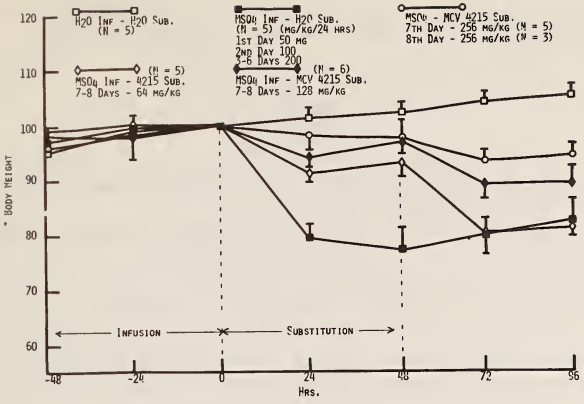
MCV 4215 did not substitute for morphine in the dose range of 1.2-38.4 mg/kg. At the higher doses, convulsions were noted in 2 monkeys which were terminated by morphine and pentobarbital injections. Much less retching was seen in the animals receiving MCV 4215 compared to those receiving vehicle.

MONKEY DATA	# ANIMALS			
B) (PPt-W)	Doses (mg/kg/sc)	3	3	3
		16.0	8.0	4.0
		Vehicle - H_2O		

MCV 4215 elicted some withdrawal signs at all doses tested. However, no retching, vomiting, and coughing were noted and little vocalization was observed when the abdomens were palpated. At the highest dose, one animal developed convulsions 20 min after receiving drug. Pentobarbital (60 mg/ip) was used to terminate those convulsions. This drug may be regarded as being a weak antagonist.

RAT INFUSION (SM)

Dose-related substitution for morphine was observed regarding weight loss and withdrawal signs (see figure and table).



Table

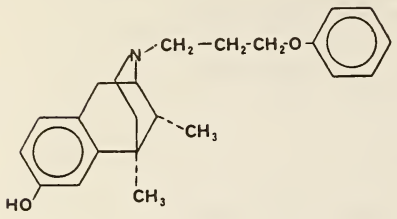
Mean Number of Withdrawal Signs[1] Noted During a 1/2 Hr Observation Period at Specific Intervals and Calculated Probability Values[2] for Comparisons Between H_2O Only Group and MCV 4215 and Morphine Controls.

	Hr in Withdrawal			
	24	48	72	96
H_2O only Group N = 5	x = 0.6	x = 1.6	x = 1.0	x = 1.4
Morphine Infusion H_2O Substitution N = 5	x = 15.2 p = 0.004	x = 16.4 p = 0.004	x = 11.4 p = 0.004	x = 10.0 p = 0.004
Morphine Infusion MCV 4215 Substitution 64 mg/kg/day N = 5	x = 0.2 p = 0.5	x = 0.6 p = 0.5	x = 18.0 p = 0.004	x = 14.0 p = 0.009
Morphine Infusion MCV 4215 Substitution 128 mg/kg/day	x = 0.8 p = 0.39	x = 1.0 p = 0.3	x = 7.0 p = 0.06	x = 9.2 p = 0.009
Morphine Infusion MCV 4215 Substitution 256 mg/kg/day, 2 of 5 rats died during infusion	x = 0.3 p = 0.14	x = 0.7 p = 0.6	x = 0.7 p = 0.6	x = 5.0 p = 0.04

1) Hypersensitivity, squealing, aggression, wet dog shakes, rubbing and chewing.

2) One-tailed test (Mann Whitney U-Test).

MCV 4216, NIH 9808, UM 1249. (+)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(3-phenoxypropyl)-6,7-benzomorphan hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - 59.6 (8.4 - 421.1)

2) TF vs M - Inactive at 10.0 and 30.0

3) PPQ - 0.5 (0.2 - 1.5)

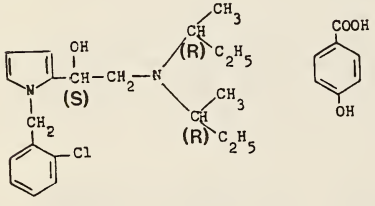
4) HP - 8.7 (6.3 - 12.0)

5) N - 11.7 (8.0 - 17.3)

MONKEY DATA (SDS) # ANIMALS Doses (mg/kg/sc) 3 / 24.0, 3 / 12.0, 3 / 3.0
Vehicle - H_2O

In the dose range studied, the drug did not substitute for morphine. Some body sag was seen in one monkey at the highest dose and in another at the lowest dose.

MCV 4224, NIH 8893, UM 1009. (-)-o-Chlorobenzyl-2-(2-di-sec-butylamino-1-hydroxyethyl)pyrrole p-hydroxybenzoate (Viminol R_2).



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - 12.8 (2.6 - 62.4)

2) TF vs M - Inactive at 1.0, 3.0, 10.0 and 30.0

3) PPQ - 2.7 (0.9 - 7.6)

4) HP - 1.2 (1.0 - 1.5)

5) N - 0.7 (0.5 - 0.9)

A) MONKEY DATA (SDS) # ANIMALS Doses (mg/kg/sc) 2 / 36.0, 3 / 24.0, 3 / 12.0, 1 / 6.0
(Vehicle)-Carboxymethylcellulose aqueous solution

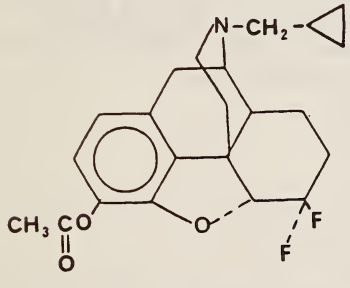
Given subcutaneously, MCV 4224 did not substitute for morphine in the dose range of 6.0 to 36.0 mg/kg.

MCV 4224, NIH 8893, UM 1009 (Cont'd)

B) MONKEY DATA (SDS) — # ANIMALS / Doses (mg/kg/iv): 3 / 2.0, 3 / 1.0, 3 / 0.5, - Vehicle
Kollidon 17 in saline, ½ ml/kg

Given intravenously, MCV 4224 substituted completely for morphine. Overall, the drug acted promptly and its duration of action was approximately 1 hr. With regard to the suppression of the important withdrawal sign designated, "vocalizes when abdomen palpated", this compound acted in a dose-related manner, i.e., at the high dose none of the monkeys vocalized, at the intermediate dose 2 of 3 did not vocalize and at the low dose 1 of 3 did not vocalize. This effect lasted for about 1 hr and by 90 min all but one of the 9 animals receiving MCV 4224 vocalized. On the other hand, morphine sulfate at 1.0 mg/kg i.v. was ineffective in suppressing vocalization during the first 30 min but was effective in 2 of 3 animals at 60 and 90 min. Retching, another withdrawal sign, was suppressed throughout the entire 2½ hr observation period at the highest dose of MCV 4224. At the 2 lower doses, retching was suppressed for the first 90 min. Morphine was effective in this respect during the entire observation period.

MCV 4230, NIH 9874, UM 1322. 3-Acetoxy-17-cyclopropylmethyl-4,5α epoxy-6,6-difluoromorphinan.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - Inactive at 1.0 and 30.0

2) TF vs M - 0.0008 (0.0002 - 0.0028)

3) PPQ - 0.1 (0.02 - 0.9)

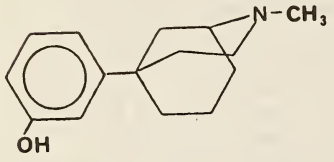
4) HP - 30% at 20.0, 10% at 50.0 and 20% at 100.0

5) N - 19.8 (12.9 - 30.2)

MONKEY DATA (PPt-W) — # ANIMALS / Doses (mg/kg/sc): 2 / 0.1, 2 / 0.05, 1 / 0.01, 1 / 0.008,
Vehicle - H_2O

This drug precipiated withdrawal at the 3 higher doses. The onset of action was prompt and the duration about 2 1/2 hr compared to 1 1/2 hr for naloxone. The potency is approximately equal to that of naloxone.

MCV 4231, 4240 NIH 9882 and 8508, UM 809, 1283. (-)-5-(m-Hydroxyphenyl)-2-methylmorphan hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - a) 5.4 (2.1 - 13.9), b) 6.1 (1.9 - 19.3), c) 21% at 1.0, 23% at 3.0, 34% at 10.0 and 53% at 30.0

2) TF vs M - a) 0% at 1.0 and 30.0, b) 27% at 1.0 and 21% at 30.0, c) Inactive at 1.0 and 30.0

3) PPQ - a) 0.9 (0.03 - 2.4), b) 0.9 (0.4 - 2.0), c) 1.3 (0.3 - 6.0)

4) HP - a) 1.7 (1.2 - 2.4), b) 2.0 (1.4 - 2.8)

RAT INFUSION (SM, HBr Salt)

As shown in the Figure, at 200 and 400 mg/kg/24 hours, MCV 4231 did not suppress weight loss during the abrupt withdrawal of morphine in morphine-dependent rats. Regarding behavioral withdrawal signs, when the MCV 4231 groups are compared to the group receiving H_2O only (Table 1) significant differences were calculated. However; when the groups receiving MCV 4321 are compared to the morphine control groups (Table 2) significant differences can also be shown. We interpret these data to mean that MCV 4231 produced a partial suppression of behavioral withdrawal signs. MCV 4231 does not readily substitute for morphine in dependent rats.

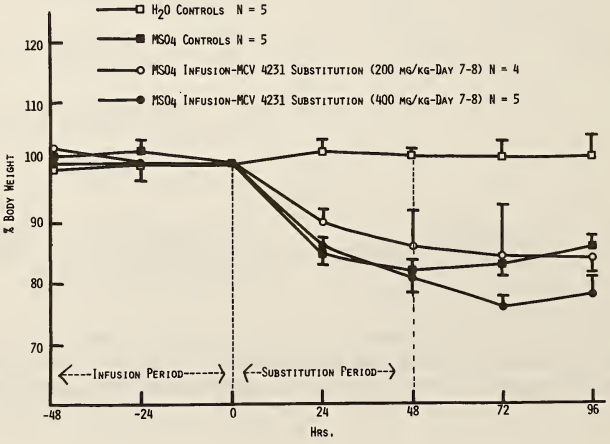


Table 1

Mean Number of Withdrawal Signs[1] Noted During the 1/2 Hr Observation Period at Specified Intervals and Calculated Probability Values[2] for Comparisons Between H_2O Only Group and MCV 4231 Group and Morphine Control.

	Hr in Withdrawal			
	24	48	72	96
H_2O only N = 5	x = 2.0	x = 1.0	x = 0.4	x = 1.2
Morphine Controls N = 5	x = 10.4 p = 0.004	x = 11.0 p = 0.008	x = 13.8 p = 0.004	x = 10.2 p = 0.004
Morphine Infusion MCV 4231 Subst. (400 mg/kg) N = 5	x = 5.2 p - 0.111	x = 17.6 p = 0.004	x = 8.6 p = 0.004	x = 6.8 p = 0.028
Morphine Infusion MCV 4231 Subst. (200 mg/kg) N = 4	x = 7.5 p = 0.347	x = 7.5 p = 0.032	x = 9.0 p = 0.008	x = 5.5 p = 0.024

Table 2

Mean Number of Withdrawal Signs[1] Noted During 1/2 Hr Observation Period at Specified Intervals and Calculated Probability Values[2] for Comparisons Between MSO_4 Group and MCV 4231 Group.

	Hr in Withdrawal			
	24	48	72	96
Morphine Control N = 5	x = 10.4	x = 11.0	x = 13.8	x = 10.2
MCV 4231 Subst. (200 mg/kg) N = 4	x = 7.5 p = 0.175	x = 7.5 p = 0.278	x = 9.0 p = 0.075	x = 5.5 p = 0.048
MCV 4231 Subst. (400 mg/kg) N = 5	x = 5.2 p = 0.028	x = 17.6 p = 0.111	x = 8.6 p = 0.016	x = 6.8 p = 0.274

1) Hypersensitivity, squealing, aggression, wet dog shakes, rubbing and chewing.

2) One-tailed test (Mann Whitney U-Test).

MCV 4232, NIH 8509, UM 810 - (+)-5-(m-Hyproxyphenyl-2-methyl-morphan Hydrochloride.

See MCV 4231
Optical isomer

MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - 4.8 (1.5 - 15.1)
2) TF vs M - 0% at 1.0, 18% at 30.0
3) PPQ - 0.5 (0.3 - 0.9)
4) HP - 0.35

Rat Infusion (SM, HBr Salt)

At 200 mg/kg/24 hr, MCV 4232 suppressed withdrawal signs (table) and when the drug was discontinued a typical opiate withdrawal syndrome was seen. The drug was partially effective in supressing weight loss (See figure). When the drug was discontinued, weight loss again accelerated. MCV 4232 appears to substitute for morphine.

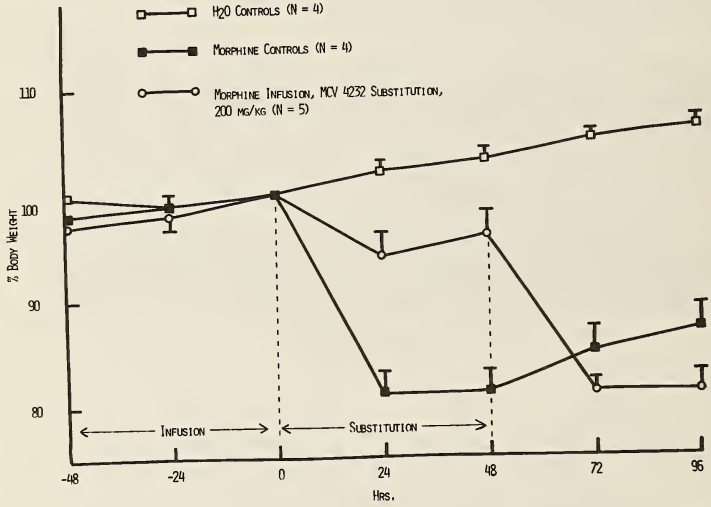
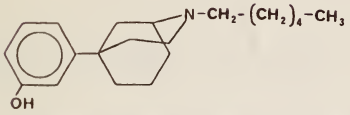


Table 1

Mean Number of Withdrawal Signs Noted During a 1/2 Hour Observation Period at Specified Intervals and Calculated Probability Values for Comparisons Between H_2O Only Group and MCV 4232 and Morphine Control.

	Hours			
	24	48	72	96
H_2O only Group	x = 1.8	x = 1.3	x = 0.5	x = 1.5
Morphine Infusion	x = 14.8	x =18.5	x = 21.0	x = 13.8
H_2O Substitute	p = 0.014	p = 0.014	p = 0.029	p = 0.057
Morphine Infusion	x = 2.0	x = 0.8	x = 7.8	x = 11.0
MCV 4232 Substitution	p = 0.548	p = 0.452	p = 0.008	p = 0.014

MCV 4234, NIH 9887. (-)-N-Hexyl-5-(m-hydroxyphenyl)morphan hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

1) TF - Inactive at 1.0, 3.0, 10.0 and 30.0

2) TF vs M - 2.1 (0.9 - 4.7)

3) PPQ - 20.2 (4.7 - 88.2)

4) HP - Inactive; toxic at 50.0

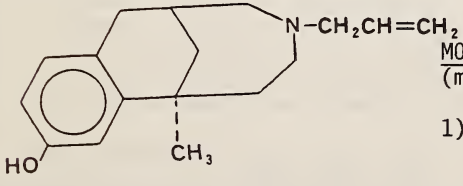
MONKEY DATA	# ANIMALS	
A) (SDS)	Doses (mg/kg/sc)	2 / 0.08, 2 / 0.31, 1 / 1.25, Vehicle-alcohol, Tween 80 and H_2O

The compound did not substitute for morphine and may have exacerbated withdrawal at the two higher doses. In the preliminary study after 2.5 mg/kg, the monkey developed severe retching and was given morphine to alleviate this distressing symptom.

MONKEY DATA	# ANIMALS	
B) (PPt-W)	Doses (mg/kg/sc)	2 / 0.08, 2 / 0.31, 1 / 1.25, Vehicle-alcohol, Tween 80 and H_2O

MCV 4234 precipitated withdrawal in a dose-related manner. The onset and duration of action were similar to naloxone. The potency is about 1/6 that of naloxone.

MCV 4236, NIH 9896, UM 1291. (-)-4-Allyl-10-hydroxy-1-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine.



MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

1) TF - Inactive at 0.3, 1.0, 10.0 and 30.0

2) TF vs M - 6.7 (3.2 - 13.7)

3) PPQ - 4.3 (1.4 - 13.1)

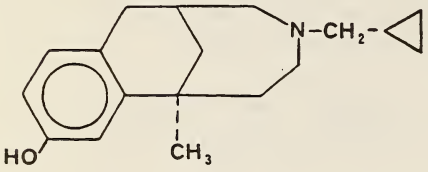
4) HP - 0% at 20.0, 40% at 50.0, convulsions

5) N - Inactive at 5.0

MONKEY DATA (PPt-W)	# ANIMALS Doses (mg/kg/sc)	3 / 4.0, 3 / 1.0, 3 / 0.25, Vehicle - H_2O

The compound did not precipitate withdrawal in morphine-dependent monkeys. Dose-related drowsiness, ataxia and tremor were noted. One monkey receiving the highest dose was not able to sit and appeared unconscious 10 min after receiving the drug. The animal was given naloxone and appeared to recover within 15 min.

MCV 4237, NIH 9899, UM 1292. (+)-4-Cyclopropylmethyl-10-hydroxyl-1-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - 0% at 1.0, 3.0, 10.0 and 30.0

2) TF vs M - 1.5 (0.5 - 4.2)

3) PPQ - 4.7 (1.9 - 11.0)

4) HP - No dose-response

MONKEY DATA A) (SDS)	# ANIMALS Doses (mg/kg/sc)	3 / 1.0, 2 / 0.25, 3 / 0.06, Vehicle-dil HCl and H_2O

The drug substituted partially for morphine at all doses. Severe ataxia, slowing, incoordination, and staring were noted at the highest dose. In the preliminary study, in one monkey given 1.0 mg/kg the following signs were noted: ataxia, catalepsy, lying on side, unable to walk. The animal was able to move about after 1 hr.

MONKEY DATA B) (PPt-W)	# ANIMALS Doses (mg/kg/sc)	1 / 1.0, 2 / 0.5, 1 / 0.25, Vehicle-dil HCl

The drug did not precipitate withdrawal. Severe ataxia was noted at the highest dose; the animal could not sit on the perch. Drowsiness, body sag, and initially some restlessness were also noted. At the intermediate doses, drowsiness, ataxia and body sag were seen at the lowest dose, drowsiness was still evident.

MCV 4238, NIH 9900, UM 1293. (-)-4-Cyclopropylmethyl-10-hydroxy-1-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine.

See MCV 4237
(Optical isomer)

MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

1) TF - 25% at 1.0, 0% at 30.0

2) TF vs M - 0% at 1.0, 17% at 10.0, 29% at 30.0

3) PPQ - 0.02 (0.007 - 0.08)

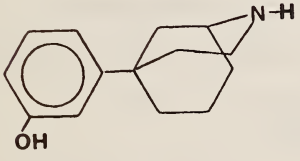
4) HP - 10% at 20.0 and 20% at 50.0

5) N - Insufficient activity at 50.0, 0% at 20.0, 25% at 50.0

MONKEY DATA (PPt-W) # ANIMALS Doses (mg/kg/sc) 2 , 2 , 1 , Vehicle-dil HCl
5.0 1.25 0.3

In the dose range tested, MCV 4238 did not precipitate withdrawal. Tremor, ataxia, drowsiness, body sag and slowing were noted as was drowsiness.

MCV 4239, NIH 9881, UM 1282. (-)-5-(m-Hydroxyphenyl)morphan hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

1) TF - 0% at 1.0 and 30.0

2) TF vs M - 0% at 1.0 and 12% at 30.0

3) PPQ - 0% at 1.0, 3.0, 10.0 and 30.0

4) HP - No dose-response

MCV 4240 and 4231, NIH 9882 and 8508, UM 1283 and 809. (-)-5-(m-Hydroxyphenyl)-2-methylmorphan hydrochloride.

MCV 4240 is identical with MCV 4231.

MCV 4243, NIH 9888. (+)-5-(m-Hydroxyphenyl)morphan hydrochloride.

See MCV 4239
(Optical isomer)

MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

1) TF - Inactive at 1.0 and 30.0

2) TF vs M - Inactive at 1.0 and 30.0

3) PPQ - 0% at 1.0, 8% at 10.0 and 57% at 30.0

4) HP - No dose-response

MCV 4244, NIH 9889, UM 1288. (+)-5-(m-Hydroxyphenyl)-2-methyl-morphan hydrochloride.

See MCV 4231
(Optical isomer)

MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

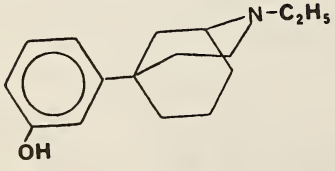
1) TF - 0.4 (0.1 -1.4)

2) TF vs M - Inactive at 1.0 and 30.0

3) PPQ - 0.2 (0.03 - 1.6)

4) HP - 0.6 (0.5 - 0.7)

MCV 4245, NIH 9890, UM 1289. (+)-2-Ethyl-5-(m-hydroxyphenyl) morphan hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

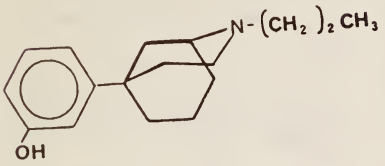
1) TF - Inactive at 1.0 and 10.0

2) TF vs M - 27% at 0.3, 40% at 0.1, 43% at 0.3, 10% at 10.0, 10% at 10.0 and 0% at 30.0

3) PPQ - Approximately 28.0

4) HP - 15.8 (12.1 - 20.5)

MCV 4246, NIH 9891, UM 1275. (+)-5-(m-Hydroxyphenyl)-2-n-propylmorphan hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

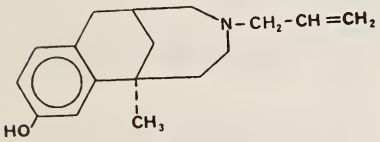
1) TF - Inactive at 1.0 and 30.0

2) TF vs M - 20% at 1.0 and 17% at 30.0

3) PPQ - 2.5 (0.9 - 7.6)

4) HP - 9.2 (6.4 - 13.0)

MCV 4248, NIH 9897, UM 1279. (+)-1-Methyl-4-allyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

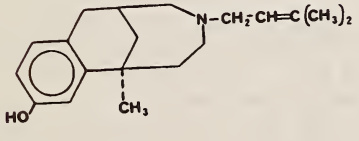
1) TF - Inactive at 1.0 and 30.0

2) TF vs M - 1.1 (0.3 - 3.9)

3) PPQ - 0.4 (0.1 - 1.2)

4) HP = 40% at 10.0, 80% at 20% Toxic at 20.0

MCV 4252, NIH 9904, UM 1278. (-)-1-Methyl-4-isopentenyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

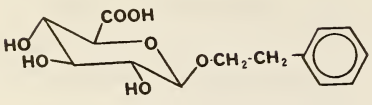
1) TF - Inactive at 1.0 and 30.0

2) TF vs M - Inactive at 1.0 and 30.0

3) PPQ - 17.3 (7.1 - 42.3)

4) HP - 20% at 2.0, 30% at 50.0 - Convulsions

MCV 4253, NIH 9921. β-Phenethyl-glucopyranosiduronic acid, Potassium salt.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - Inactive at 1.0 and 30.0

2) TF vs M - 17% at 0.3, 33% at 1.0, 20% at 3.0 and 0% at 30.0

3) PPQ - 2.5 (1.0 - 6.6)

4) HP - 10% at 20.0, 0% at 50.0 and 100.0

MCV 4254, NIH 9903, UM 1315. (+)-1-Methyl-4-isopentenyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine.

MOUSE DATA -ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - Inactive at 1.0 and 30.0

See MCV 4252 (Opitcal isomer)

2) TF vs M - 27% at 1.0, 45% at 10.0, 55% at 30.0

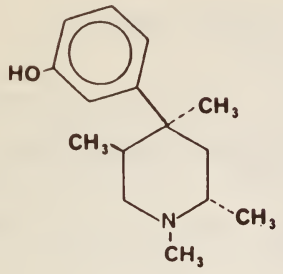
3) PPQ - 1.8 (0.6 - 5.4)

4) HP - 10.1 (7.1 - 14.4)

MONKEY DATA (SDS) # ANIMALS Doses (mg/kg/sc) 1/1.0, 3/5.0, 3/10.0
Vehicle-dil HCl and H_2O

MCV 4254 did not substitute for morphine in the dose range tested. However, the drug reduced the incidence of the withdrawal signs retching and vomiting. At the highest dose, ataxia, nystagmus, myoclonic jerks and miosis were noted. In the preliminary study at a cummulative dose of 15 mg/kg in 30 min, the animal was severely uncoordinated and could not climb to the perch.

MCV 4259, NIH 9922. 3-(1,2α,4α,5β-Tetramethyl-4β-piperidinyl)-m-phenol, z-2-butenedioic acid salt.



MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

1) TF - 2.9 (0.8 - 10.6)

2) TF vs M - 18% at 1.0, 15% at 3.0, 5% at 10.0 and 0% at 30.0

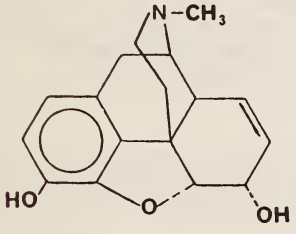
3) PPQ - 0.5 (0.2 - 1.4)

4) HP - 2.4 (1.7 - 8.3)

MONKEY DATA (SDS) # ANIMALS Doses (mg/kg/sc) 3 / 1.5, 3 / 3.0, 2 / 6.0, Vehicle-H_2O

MCV 4259 substituted completely and briefly for morphine in all the animals at the highest dose. The onset of action was rapid. At the intermediate dose, the drug substituted as above in 2 of 3 monkeys. The drug is estimated to be 1/4 - 1/2 as potent as morphine.

MCV 4260, NIH 9929 and 0001, UM 1311 and 114. Morphine.



MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

1) TF - 5.0 (2.9 - 8.9)

2) TF vs M - Inactive 1.0 and 30.0

3) PPQ - 0.1 (0.03 - 0.3)

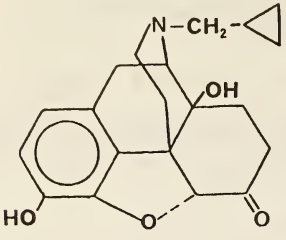
4) HP - 0.9 (0.6 - 1.2)

5) N - 1.3 (1.0 - 1.9)

MONKEY DATA (SDS) # ANIMALS Doses (mg/kg/sc) 1 / 2.5, 1 / 5.0, 2 / 10.0, 1 / 20.0, Vehicle-dil HCL and H_2O

At the 2 higher doses, MCV 4260 substituted completely for morphine. The drug has a quick onset and a long duration of action (> 5 hr). Some drowsiness noted at the 10.0 mg/kg dose. Drug supply was exhausted.

MCV 4261 and 4002, NIH 9930 and 8503, UM 1312 and 792. Naltrexone hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

1) TF - Inactive 1.0 and 30.0

2) TF vs M - 0.001 (0.0004 - 0.004)

3) PPQ - Inactive at 1.0 and 30.0

4) HP - 10% at 20.0, 40% at 50.0

MONKEY DATA	# ANIMALS				
A) (SDS)	Doses (mg/kg/sc)	1	3	3	
		0.00015	0.006	0.0025	
					Vehicle-H_2O

MCV 4261 did not substitute for morphine. The drug may have exacerbated withdrawal at the highest dose.

MONKEY DATA	# ANIMALS					
B) (PPt-W)	Doses (mg/kg/sc)	1	2	3	2	
		0.0003	0.00125	0.005	0.015	
						Vehicle-H_2O

MCV 4261 precipitated dose-related withdrawal signs in morphine-dependent monkeys. The drug has a quick onset of action. The duration of action is approximately 1 hr longer than that of naloxone and its potency is approximate 10 x that of the reference compound (Naloxone).

MCV 4264, NIH 9905, UM 1308. (±)-1-Methyl-4-isopentenyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine.

See MCV 4252

MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

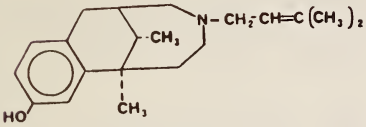
1) TF - Inactive at 1.0 and 30.0

2) TF vs M - 24% at 1.0, 16% at 30.0

3) PPQ - 6.9 (4.0 - 11.8)

4) HP - 20% at 20, 70% at 50.0

MCV 4265, NIH 9906 UM 1309. 1,12α-Dimethyl-4-isopentenyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

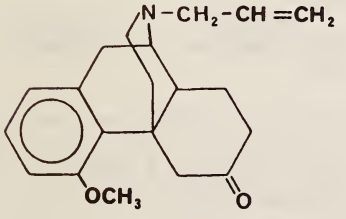
1) TF - 12.2 (4.3 - 34.9)

2) TF vs M - Inactive at 1.0 and 30.0

3) PPQ - 2.1 (0.7 - 6.2)

4) HP - 11.5 (8.9 - 15.0)

MCV 4266 and 4279, NIH 9926, UM 1310. (-)-N-Allyl-4-methoxy-morphinan-6-one.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

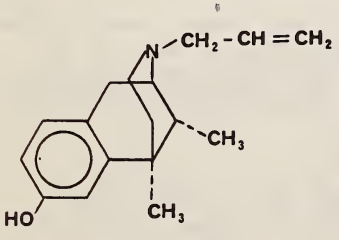
1) TF - 4.7 (1.8 - 12.7)

2) TF vs M - 0% at 1.0 and 30.0

3) PPQ - 1.0 (0.3 - 2.9)

4) HP - 20% at 20.0, 30% at 50.0

MCV 4267, NIH 7912, UM 902. (±)-2-Allyl-2'-hydroxy-5,9α-dimethyl-6,7-benzomorphan hydrochloride (SKF-10,047).



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - Inactive at 1.0 and 30.0

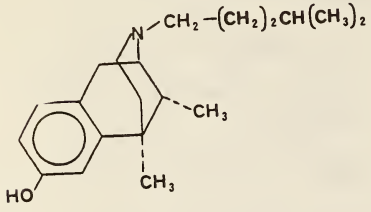
2) TF vs M - 0.1 (0.004 - 0.4)

3) PPQ - 1.6 (0.6 - 4.6)

4) HP - Inactive

5) N - 16.1 (10.9 - 23.7)

MCV 4269, NIH 9938. 5,9 α-Dimethyl-2'-hydroxy-2-(4-methyl-pentyl)-6,7-benzomorphan hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

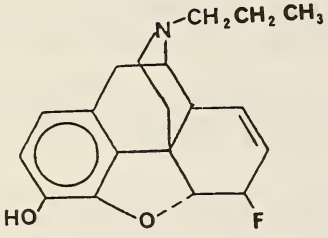
1) TF - 3.3 (1.5 - 7.3)

2) TF vs M - 0% at 1.0 and 30.0

3) PPQ - 2.6 (1.0 - 7.9)

4) HP - 8.3 (6.0 - 11.4)

MCV 4270, NIH 9939, UM 1330. 6,7-Didehydro-4,5α-epoxy-6-fluoro-3-hydroxy-17-n-propylmorphinan.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - Inactive at 1.0 and 30.0

2) TF vs M - 0.4 (0.1 - 1.4)

3) PPQ - 13% at 3.0, 38% at 10.0 and 49% at 30.0

4) HP - Insufficient activity, toxic at 100.0

MONKEY DATA	# ANIMALS	
A) (SDS)	Doses (mg/kg/sc)	1 / 1.25, 2 / 0.3, 1 / 0.08

Vehicle - alcohol, Tween 80, H_2O

In the preliminary study, the monkey developed severe tremors after receiving 5.0 mg/kg. The animal was given morphine twice to alleviate severe withdrawal in the regular SDS study, MCV 4270 did not substitute for morphine in the dose range tested and appeared to exacerbate withdrawal.

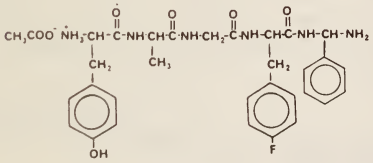
MONKEY DATA	# ANIMALS	
B) (PPt-W)	Doses (mg/kg/sc)	1 / 1.25, 3 / 0.3, 2 / 0.08, 1 / 0.02

Vehicle - alcohol, Tween 80, H_2O

MCV 4270, NIH 9939, UM 1330, (Cont'd)

MCV 4270 precipitated withdrawal signs at the 3 higher doses. Its action was prompt and lasted 30-60 min longer than that of naloxone. The drug is estimated to be about 2/3 as active as naloxone.

MCV 4271, NIH 9947. L-Tyrosyl-D-alanylglycyl-L-4-fluoro-phenylalanyl-L-phenylglycinamide acetate.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - 15.4 (5.3 - 44.8)

2) TF vs M - Inactive at 1.0 and 30.0

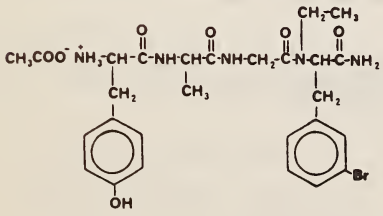
3) PPQ - 0.06 (0.03 - 0.09)

4) HP - 2.1 (7.5 - 3.0)

MONKEY DATA (SDS)	# ANIMALS Doses (mg/kg/sc)	3/8.0, 5/4.0, 5/2.0, 2/1.0 Vehicle - H_2O

At the 8.0 mg/kg dose, MCV 4271 substituted completely for morphine. Drowsiness was also observed in one monkey at this dose. The onset of action was delayed for 1/2 hr and the duration of action was brief (60-90 min). At 4.0 and 2.0 mg/kg the drug substituted briefly for morphine in 2 monkeys at each dose and drowsiness was noted in all the animals. This compound is about 1/3 as active as morphine.

MCV 4272, NIH 9948. L-Tyrosyl-D-alanylglycyl-N-α-ethyl-L-m-bromo-phenylalanine amide acetate.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - 11.3 (3.1 - 40.8)

2) TF vs M - Inactive at 1.0 and 30.0

3) PPQ - 0.5 (0.2 - 1.6)

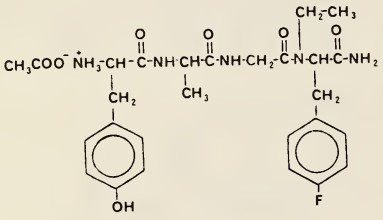
4) HP - 3.3 (2.3 - 4.9)

MCV 4272, NIH 9948 (Cont'd)

MONKEY DATA (SDS)	# ANIMALS Doses (mg/kg/sc)	2 , 3 , 3 , 1 , 8.0 4.0 1.0 0.25 Vehicle - H_2O

At 8.0 mg/kg, the drug substituted completely in one of two monkeys for about 2 hr. At 4.0 mg/kg; the drug substituted completely in 1 of 3 monkeys for the same length of time. Some drowsiness was observed at all doses but the lowest. Exhaustion of drug supply precluded a full evaluation of the compound.

MCV 4273, NIH 9949. N-α-Methyl-L-tyrosyl-D-alanylglycyl-N-α-ethyl-L-p-fluorophenylalanine amide acetate.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - 2.5 (1.1 - 5.7)

2) TF vs M - Inactive at 1.0 and 30.0

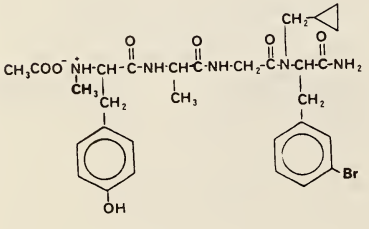
3) PPQ - 0.06 (0.02 - 0.2)

4) HP - 0.7 (0.5 - 1.0)

MONKEY DATA (SDS)	# ANIMALS Doses (mg/kg/sc)	3 , 3 , 2 , Vehicle-H_2O 3.0 1.5 0.75

At the highest dose, MCV 4273 briefly suppressed all withdrawal signs; however, drowsiness was evident in 2/3 animals. The onset of action was < 30 min and the duration of action was approximately 2 hr. At lower doses, the drug partially suppressed withdrawal. Retching was the main sign suppressed. Approximately equipotent with morphine.

MCV 4274, NIH 9950. N-α-Methyl-L-tyrosyl-D-alanylglycyl-N-α-cyclopropylmethyl-L-m-bromophenylalanine amide acetate.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - 11.8 (5.5 0 25.3)

2) TF vs M - Inactive at 1.0 and 30.0

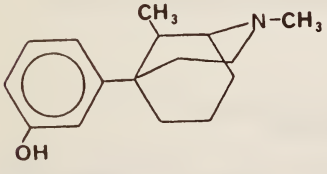
3) PPQ - 0.02 (0.002 - 0.16)

4) HP - 2.1 (1.1 - 4.2)

MONKEY DATA (SDS)	# ANIMALS Doses (mg/kg/sc)	2 / 10.0, 2 / 5.0, 1 / 2.5, 1 / 1.25, Vehicle - H_2O

MCV 4274 substituted completely but briefly (1 to 2 hr) for morphine at the 3 higher doses. Drowsiness was noted in many of the animals at these doses. Approximately equipotent with morphine.

MCV 4275, NIH 9955. (±)-2,9 α-Dimethyl-5-(m-hydroxyphenyl)morphan hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - Inactive at 1.0 and 30.0

2) TF vs M - 5.0 (2.0 - 12.8)

3) PPQ - 19% at 1.0 and 28% at 30.0

4) HP - 9.3 (6.4 - 13.5)

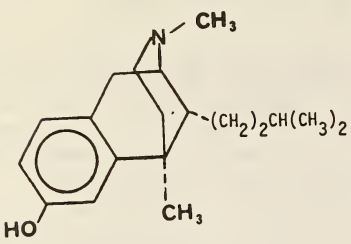
MONKEY DATA A) (SDS)	# ANIMALS Doses (mg/kg/sc)	1 / 4.0, 2 / 1.0, 1 / 0.25, Vehicle-H_2O

In the dose range tested, the compound did not substitute for morphine.

MONKEY DATA B) (PPt-W)	# ANIMALS Doses (mg/kg/sc)	2 / 4.0, 2 / 1.0, 2 / 0.25, Vehicle-H_2O

At the highest dose, MCV 4275 precipitated withdrawal. The onset of action was prompt and the duration like that of naloxone. The drug is about 1/80 as active as naloxone.

MCV 4276, NIH 9450, UM 1305. 2,5-Dimethyl-2'-hydroxy-9α-isopentyl-6,7-benzomorphan methanesulfonate.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - Inactive at 1.0 and 30.0

2) TF vs M - Inactive at 1.0 and 30.0

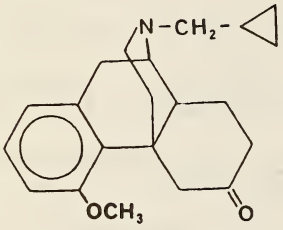
3) PPQ - 13.8 (4.6 - 41.4)

4) HP - 14.1 (11.7 - 17.0)

5) N - 19.7 (13.4 - 29.0)

MCV 4279 (See MCV 4266) - Note MCV 4266 is identical with MCV 4279.

MCV 4280, NIH 9931, UM 1313. (-)-N-Cyclopropylmethyl-4-methoxy-morphinan-6-one.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - 16% at 1.0 and 14% at 30.0

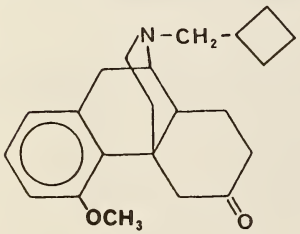
2) TF vs M - 0.4 (0.1 - 1.6)

3) PPQ - 1.2 (0.3 - 4.1)

4) HP - 21.7 (17.9 - 26.3)

5) N - 0% at 10.0, 40% at 20.0

MCV 4281, NIH 9932, UM 1314. (-)-N-Cyclobutylmethyl-4-methoxy-morphinan-6-one hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - Inactive at 1.0 and 30.0

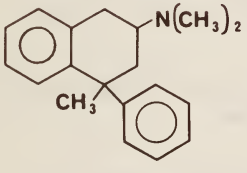
2) TF vs M - 10.0 (2.5 - 40.1)

3) PPQ - 0.7 (0.3 - 1.8)

4) HP - 50% at 20.0 6/10 convulsions at 50.0

5) N - 3.6 (2.5 - 5.4)

MCV 4282, NIH 9940. (±)-trans-N,N-Dimethyl-1,2,3,4-tetrahydro-4-methyl-4-phenyl-2-naphthylamine hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - Inactive at 1.0 and 30.0

2) TF vs M - Inactive 1.0 and 30.0

3) PPQ - 4.4 (1.4 - 14.3)

4) HP - 0% at 20.0, 20% at 50.0 and 60% at 100.0

MCV 4283, NIH 9941. (-)-trans-N,N-Dimethyl-1,2,3,4-tetra-hydro-4-methyl-4-phenyl-2-naphthylamine hydrochloride.

See MCV 4282
(Optical isomer)

MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - Inactive at 1.0 and 30.0

2) TF vs M - Inactive at 1.0 and 30.0

3) PPQ - 3.0 (1.2 - 7.6)

4) HP - 13.1 (9.9 - 17.3)

MCV 4284, NIH 9942. (+)-trans-N,N-Dimethyl-1,2,3,4-tetra-hydro-4-methyl-4-phenyl-2-naphthylamine hydrochloride.

See MCV 4282
(Optical isomer)

MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

1) TF - Inactive at 1.0 and and 30.0

2) TF vs M - Inactive at 1.0 and 30.0

3) PPQ - 2.3 (0.9 - 6.1)

4) HP - 0% at 20.0, 40% at 50.0 and 30% at 100.0

MCV 4285, NIH 9943. (-)-cis-N,N-Dimethyl-1,2,3,4-tetra-hydro-4-methyl-4-phenyl-2-naphthylamine hydrochloride.

See MCV 4282
(Geometric isomer)

MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

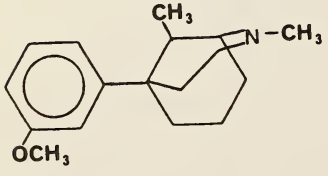
1) TF - Inactive at 1.0 and 30.0

2) TF vs M - Inactive at 1.0 and 30.0

3) PPQ - 1.9 (0.5 - 7.3)

4) HP - 5.6 (3.8 - 8.1)

MCV 4286, NIH 9945, UM 1327. (±)-2,9α-Dimethyl-5-(m-methoxyphenyl) morphan hydrobromide.



MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

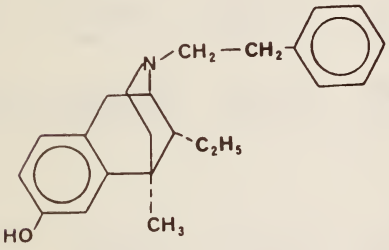
1) TF - Inactive at 1.0 and 30.0

2) TF vs M - 0% at 1.0, 30% at 30.0

3) PPQ - 2% at 10.0 and 42% at 30.0

4) HP - 10% at 20.0, 50% at 50.0

MCV 4288, NIH 9454, UM 1146. 9α -Ethyl-2'-hydroxy-5-methyl-2-phenethyl-6,7-benzomorphan.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - 6.3 (0.2 - 239.9)

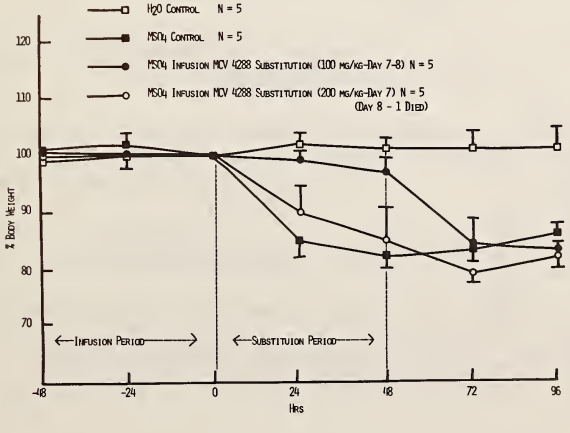
2) TF vs M - 4% at 1.0, 0% at 10.0, 58% at 30.0

3) PPQ - 0.1 (0.006 - 0.3)

4) HP - 0.7 (0.6 - 0.9)

RAT INFUSION (SM)

Although MCV 4288 did not completely suppress weight loss in abruptly withdrawn morphine-dependent rats, it completely suppressed behavioral withdrawal signs. When the drug was discontinued weight loss was more precipitous and behavioral signs of withdrawal were evident. The drug substitutes for morphine but additional doses should be tested. Weight loss shown in Fig. and withdrawal sign evaluation in table.



Table

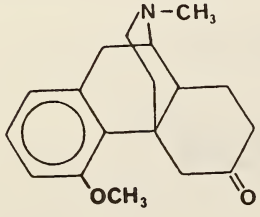
Mean Number of Withdrawal Signs[1] Noted During 1/2 Hr Observation Period at Specified Intervals and Calculated Probability Values[2] for Comparisons Between H_2O Only Group and MCV 4288 Group and Morphine Control.

	Hr in Withdrawal			
	24	48	72	96
H_2O only N = 5	x = 2.0	x = 1.0	x = 0.4	x = 1.2
Morphine Controls N = 5	x = 10.4 p = 0.004	x = 11.0 p = 0.008	x = 13.8 p = 0.004	x = 10.2 p = 0.004
Morphine Infusion MCV 4288 Subst. (200 mg/kg) N = 4 (1 out of 5 died)	x = 2.8 p = 0.409	x = 3.8 p = 0.044	x = 7.5 p = 0.076	x = 5.5 p = 0.119
Morphine Infusion MCV 4288 Subst. (100 mg/kg) N = 5	x = 3.8 p = 0.345	x = 7.8 p = 0.155	x = 13.0 p = 0.004	x = 11.4 p = 0.012

1) Hypersensitivity, squealing, aggression, wet dog shakes, rubbing and chewing.

2) One-tailed tested (Mann Whitney U-Test).

MCV 4289, NIH 9927. (-)-3-Methoxy-N-methylmorphinan-6-one.



MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

1) TF - 0.3 (0.1 - 0.6)

2) TF vs M - Inactive at 1.0 and 30.0

3) PPQ - 0.005 (0.001 - 0.160)

4) HP - 1.1 (0.9 - 1.4)

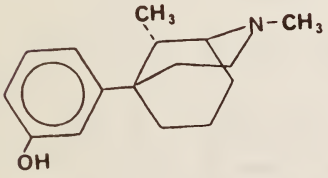
5) N - 0.4 (0.3 - 0.6)

MCV 4289, NIH 9927 (Cont'd)

MONKEY DATA (SDS)	# ANIMALS Doses (mg/kg/sc)	1 / 2.0 , 2 / 1.0 , 1 / 0.5 , 2 / 0.25 , 1 / 0.06 , Vehicle-DMSO and H_2O

At all doses but the lowest dose, MCV 4289 substituted completely for morphine. The onset of action was prompt. In one monkey receiving 1.0 mg/kg, the duration of action was about 7 1/2 hr. The duration of action of the two active lower doses was about 1 hr. Drowsiness was seen at all the active doses, except at the highest dose. In one non-dependent animal receiving the compound, all drug-induced signs such as sagging, drowsiness, slowing, ataxia were reversed by 1.0 mg/kg of naloxone. Approximately 10 times more potent than morphine.

MCV 4293, NIH 9971. (-)-2,9α - Dimethyl-5-(m-hydroxyphenyl)morphan hydrochloride).



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - Inactive at 1.0 and 30.0

2) TF vs M - Inactive at 1.0 and 30.0

3) PPQ - 1.9 (0.4 - 8.5)

4) HP - 40% at 20.0, 60% at 50.0

5) N - 0% at 20.0 and 25% at 50.0

MONKEY DATA A) (SDS)	# ANIMALS Doses (mg/kg/sc)	2 / 10.0 , 2 / 5.0 , 2 / 2.5 , Vehicle-H_2O

This compound did not substitute for morphine. At the highest dose, both animals showed severe tremors; at lower doses tremors were evident in all but one animal.

MONKEY DATA B) (PPt-W)	# ANIMALS Doses (mg/kg/sc)	2 / 10.0 , 2 / 2.5 , Vehicle-H_2O

MCV 4293 precipitated withdrawal in the dose range of 2.5-10.0 mg/kg. The drug acted promptly and its duration of action was 30-60 min. longer than that of naloxone (duration 90 min). The potency was estimated to be 1/200 that of naloxone. Drug supply was exhausted.

MCV 4294, NIH 9972. (+)-2,9α-Dimethyl-5-(m-hydroxyphenyl)morphan hydrochloride.

See MCV 4293
(Optical isomer)

MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

1) TF - Inactive at 1.0 and 30.0

2) TF vs M - 4.5 (1.7 - 11.8)

3) PPQ - Inactive at 1.0 and 30.0

4) HP - 10% at 20.0 and 50.0

5) N - Inactive at 20.0

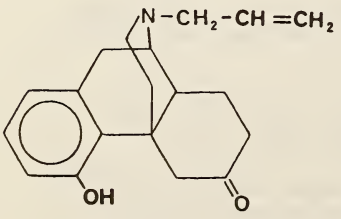
MONKEY DATA	# ANIMALS				
A) (SDS)	Doses (mg/kg/sc)	2, 8.0	2, 4.0	Vehicle-dil HCl and H_2O	

At the highest dose, the drug seemed to exacerbate withdrawal. Tremors were especially evident at this dose. The drug did not substitute for morphine.

MONKEY DATA	# ANIMALS				
B) (PPt-W)	Doses (mg/kg/sc)	2, 12.0	2, 6.0	2, 3.0	Vehicle-H_2O

MCV 4294 precipitated withdrawal at all three doses. At the highest dose, one monkey was given pentobarbital 50 min after receiving the compound to terminate severe tremors. At the lowest dose, one animal showed withdrawal. The onset of action was prompt; the duration was 30-60 min longer than that of naloxone. The potency is approximately 1/100 that of naloxone.

MCV 4295, NIH 9974. (-)-N-Allyl-4-hydroxymorphinan-6-one.



MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

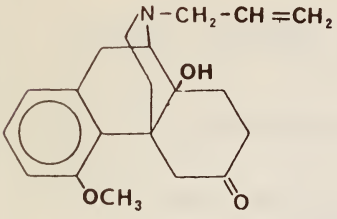
1) TF - 0.7 (0.3 - 1.6)

2) TF vs M - Inactive at 1.0 and 30.0

3) PPQ - 0.1 (0.04 - 0.3)

4) HP - 1.8 (1.5 - 3.2)

MCV 4296, NIH 9975, UM 1347. (-)-N-Allyl-14-hydroxy-4-methoxy-morphinan-6-one.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

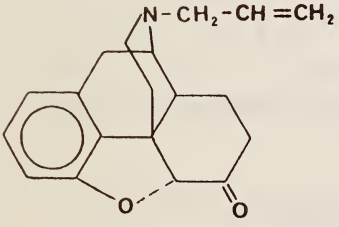
1) TF - Inactive at 1.0 and 30.0

2) TF vs M - 3.3 (1.3 - 8.8)

3) PPQ - 8.7 (1.8 - 42.6)

4) HP - 0% at 20 and 20% at 50

MCV 4297, NIH 9976. (-)-N-Allyl-4,5-epoxymorphinan-6-one.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - Inactive at 1.0 and 30.0

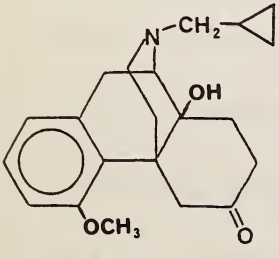
2) TF vs M - Inactive at 1.0 and 10.0

3) PPQ - 2.3 (1.1 - 5.0)

4) HP - 6.4 (4.4 - 9.5)

5) N - 8.3 (6.0 - 11.4)

MCV 4298, NIH 9977. (-)-N-Cyclopropylmethyl-14-hydroxy-4-methoxy morphinan-6-one.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - Inactive at 1.0 and 30.0

2) TF vs M - 0.9 (0.4 - 2.0)

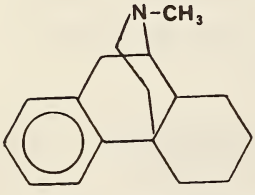
3) PPQ - 2% at 1.0 and 23% at 30.0

MCV 4298, NIH 9977 (Cont'd)

4) HP - 10% at 20.0 and 25% at 50.0

5) N - 0% at 20.0 and 25% at 50.0

MCV 4299, NIH 9989. (-)-N-Methylmorphinan d-tartrate.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - 3.9 (2.1 - 7.2)

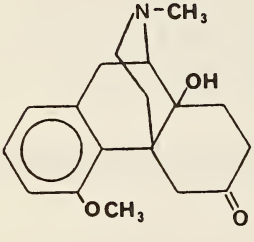
2) TF vs M - Inactive at 1.0 and 30.0

3) PPQ - 2.4 (1.3 - 4.3)

4) HP - 2.3 (1.7 - 3.2)

5) N - 2.5 (1.7 - 3.7)

MCV 4305, NIH 9959, UM 1340. (-)-14-Hydroxy-4-methoxy-N-methylmorphinan-6-one.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - a. 3.3 (1.1 - 9.6)
b. 0.6 (0.2 - 2.1)

2) TF vs M - Inactive at 1.0 and 30.0

3) PPQ - 0.04 (0.01 - 0.14)

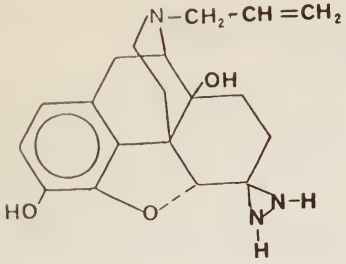
4) HP - 0.16 (0.12 - 0.21)

MCV 4308, NIH 10,001. 6-Desoxy-6,6-hydrazinaloxone.

MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - Inactive at 1.0 and 30.0

MCV 4308, NIH 10,001 (Cont'd)



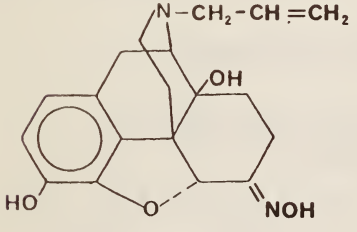
2) TF vs M - 0.06 (0.04 - 0.1)

3) PPQ - Inactive at 1.0 and 30.0

4) HP - 20% at 20.0, 0% at 50.0 and 100.0

5) N - Inactive at 100.0

MCV 4309, NIH 10,002. 6-Desoxy-6-isonitrosonaloxone.



MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

1) TF - Inactive at 1.0 and 30.0

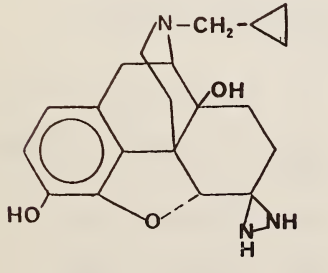
2) TF vs M - 0.06 (0.02 - 0.1)

3) PPQ - Inactive at 1.0 and 10.0

4) HP - 20% at 20.0, 50.0 and 100.0

5) N - Inactive at 100.0

MCV 4310, NIH 10,003. 6-Desoxy-6,6-hydrazinaltrexone.



MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

1) TF - Inactive at 1.0 and 30.0

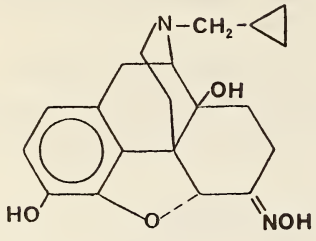
2) TF vs M - 0.02 (0.01 - 0.03)

3) PPQ - Inactive at 10.0 and 30.0

4) HP - 0% at 20.0 and 100.0

5) N - Inactive at 100.0

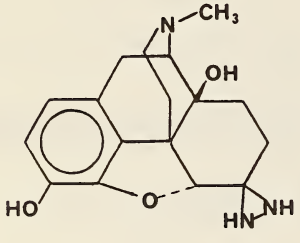
MCV 4311, NIH 10,004. 6-Desoxy-6-isonitrosonaltrexone.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - Inactive at 1.0 and 30.0
2) TF vs M - 0.08 (0.03 - 0.2)
3) PPQ - Inactive at 1.0 and 3.0
4) HP - 20% at 20.0, 50.0 and 100.0
5) N - Inactive at 100.0

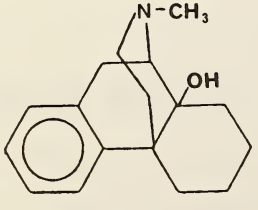
MCV 4312, NIH 10,005. 6-Desoxy-6,6-hydrazioxymorphone.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - 2.2 (1.4 - 3.6)
2) TF vs M - Inactive at 1.0 and 30.0
3) PPQ - 0.1 (0.03 - 0.4)
4) HP - 0.6 (0.4 - 0.8)
5) N - 0.5 (0.3 - 0.7)

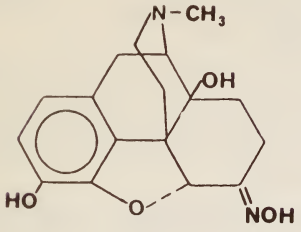
MCV 4313, NIH 10,007. (-)-14-Hydroxy-N-methylmorphinan.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - 4.7 (2.0 - 10.7)
2) TF vs M - Inactive 1.0 and 30.0
3) PPQ - 1.0 (0.4 - 2.3)
4) HP - 3.6 (2.7 - 4.8)
5) N - 4.2 (3.0 - 6.0)

MCV 4314, NIH 10,008. 6-Desoxy-6-isonitrosooxymorphone hydrobromide.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - 0.7 (0.3 - 1.7)

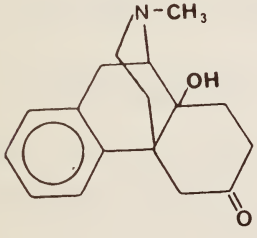
2) TF vs M - Inactive at 1.0 and 30.0

3) PPQ - 0.05 (0.01 - 0.2)

4) HP - 0.8 (0.7 - 1.0)

5) N - 2.0 (1.4 - 2.4)

MCV 4315, NIH 10,009. (-)-14-Hydroxy-N-methylmorphinan-6-one.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - 0.4 (0.2 - 0.8)

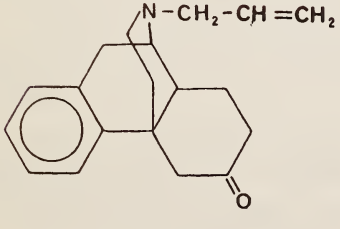
2) TF vs M - Inactive at 1.0 and 30.0

3) PPQ - 0.3 (0.1 - 0.8)

4) HP - 0.5 (0.4 - 0.7)

5) N - 0.5 (0.4 - 0.7)

MCV 4316, NIH 10,010. (-)-N-Allylmorphinan-6-one.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - 6.3 (3.5 - 11.4)

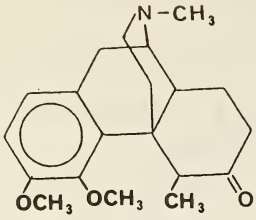
2) TF vs M - Inactive at 1.0 and 10.0

3) PPQ - 0.5 (0.2 - 1.4)

4) HP - 2.9 (2.1 - 3.9)

5) N - 1.8 (1.3 - 2.7)

MCV 4317, NIH 10,015. (-)-3,4-Dimethoxy-5,17-dimethyl-morphinan-6-one hydrobromide.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

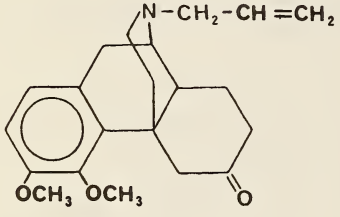
1) TF - 2.2 (0.7 - 6.8)

2) TF vs M - Inactive at 1.0 and 30.0

3) PPQ - 0.3 (0.08 - 0.81)

4) HP - 0.8 (0.6 -1.1)

MCV 4318, NIH 10,016. (-)-N-Allyl-3,4-dimethoxymorphinan-6-one.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

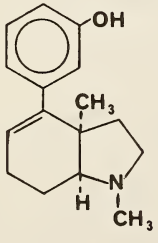
1) TF - 21% at 3.0, 39% at 10.0 and 46% at 30.0

2) TF vs M - 4.6 (1.3 - 16.1)

3) PPQ - 1.5 (0.4 - 5.0)

4) HP - 10.6 (8.0 - 14.1)

MCV 4322, NIH 10,020. 1,3aα -Dimethyl-2,3,3a,6,7,7aα -hexahydro-4-m-hydroxyphenyl-1H-indole.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF -Inactive at 1.0 and 30.0

2) TF vs M - 1.7 (0.5 - 6.6)

3) PPQ - Inactive at 1.0 and 30.0

4) HP - 40% at 20.0 and 50.0, 50% at 100.0

MCV 4322, NIH 10,020 (Cont'd)

MONKEY DATA	# ANIMALS			
A) (SDS)	Doses (mg/kg/sc)	2 / 4.0	1 / 2.0	1 / 1.0

Vehicle-dil HCl and H_2O

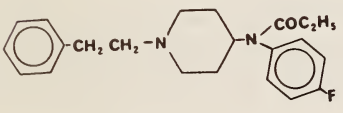
The drug did not substitute for morphine and appeared to exacerbate withdrawal. One of the monkeys at the highest dose and one receiving vehicle were given morphine to alleviate severe tremors.

MONKEY DATA	# ANIMALS			
B) (PPt-W)	Doses (mg/kg/sc)	2 / 8.0	3 / 4.0	2 / 1.0

Vehicle-dil-HCl and H_2O

This compound promptly precipitated withdrawal at the 2 higher doses. The duration of action was similar to that of naloxone. The potency is estimated at 1/80 that of naloxone.

MCV 4323, NIH 10,022. p-Fluorofentanyl hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - 0.03 (0.01 - 0.08)

2) TF vs M - Inactive at 1.0 and 30.0

3) PPQ - 0.0006 (0.00007 - 0.005)

4) HP - 0.015 (0.011 - 0.020)

MONKEY DATA	# ANIMALS				
(SDS)	Doses (mg/kg/sc)	2 / 0.04	2 / 0.01	2 / 0.003	Vehicle-H_2O

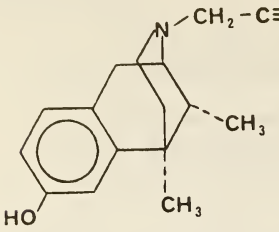
This compound substituted completely for morphine at the 2 higher doses. However, the onset of action was slightly delayed (< 30 min) and the duration was about 90 min. Some drowiness was obvious at that dose. The drug is estimated to be about 100 X as potent as morphine.

MCV 4324, NIH 10,024. α-(-)-N-Propynyl-N-normetazocine hydrobromide.

MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - Inactive at 1.0 and 30.0

MCV 4324, NIH 10,024 (Cont'd)



2) TF vs M - 0.3 (0.1 - 0.7)

3) PPQ - 0.2 (0.01 - 0.4)

4) HP - 50% at 20.0, 20% at 50.0 Toxic at 50.0

5) N - 0% at 20.0, 12% at 50.0

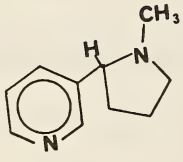
MONKEY DATA	# ANIMALS				
A) (SDS)	Doses (mg/kg/sc)	2 / 0.25	2 / 0.06	2 / 0.015	Vehicle-H_2O

MCV 4324 did not substitute for morphine. The drug exacerbated withdrawal at the 2 higher doses.

MONKEY DATA	# ANIMALS				
B) (PPt-W)	Doses (mg/kg/sc)	1 / 0.5	2 / 0.125	2 / 0.03	Vehicle-H_2O

The compound precipitated withdrawal at all doses but the lowest. The onset of action is rapid. The duration of action is about 30 min longer than that of naloxone. Naloxone is approximately 25 X more potent.

MCV 4325, NIH 9801. (+)-Nicotine di-d-tartrate.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF - 3% at 1.0 and 21% at 30.0

2) TF vs M - Inactive at 1.0 and 30.0

3) PPQ - 22% at 27.0, 44% at 90.0 and 76% at 180.0

4) HP - 23.3 (16.7 - 32.1)

5) N - 38.2 (26.2 - 55.8)

MONKEY DATA	# ANIMALS				
(SDS)	Doses (mg/kg/sc)	2 / 4.0	3 / 2.0	1 / 0.5	Vehicle-H_2O

Produced abdominal muscle relaxation and suppressed vocalization when abdomens were palpated in approximately 1/2 the animals tested at the 2 higher doses. The withdrawal sign retching was also suppressed at the highest dose. This isomer did not substitute completely for morphine. It is 1/4 to 1/5 as potent as its natural isomer. More studies are recommended.

Evaluation of New Compounds for Opioid Activity: 1982 Annual Report

James H. Woods, Jonathan L. Katz, Fedor Medzihradsky, Charles B. Smith, and Gail D. Winger

The evaluation of new compounds by the programs at the University of Michigan and the Medical College of Virginia is coordinated by Dr. Arthur E. Jacobson, Medicinal Chemistry Section, NIADDKD, National Institutes of Health, Bethesda, MD. The drugs, which come originally from pharmaceutical companies, universities, and government laboratories, are submitted to Dr. Jacobson, who performs the MOUSE ANALGESIA tests. Values obtained in these tests for some representative opioid drugs are given in Table I.

At the UM and MCV laboratories, drug samples arrive from Dr. Jacobson with only the following information: (1) an identifying NIH number, (2) molecular weight, (3) solubility information, (4) a recommended starting dose, and (5) mouse analgesia data. Only after the evaluation is completed and the report sent by Dr. Jacobson to the submitter is the chemical structure released to the evaluating laboratory.

DEPENDENCE EVALUATION IN RHESUS MONKEYS

The single-dose suppression test (SDS) determines the ability of a drug to suppress the signs of withdrawal in monkeys which have been made dependent by the chronic administration of morphine (3 mg/kg every six hours). Compounds suspected of having morphine-antagonist properties are tested for their ability to precipitate the withdrawal syndrome in nonwithdrawn (NW) morphine-dependent monkeys. Nondependent monkeys (Normals) are used to determine whether the acute effects of the test drug are reversible by nalorphine or naloxone. In a primary dependence study (PDS), nondependent monkeys receive the test drug every six hours for 30 days to determine whether withdrawal signs will appear when the animals are challenged with an antagonist or when drug administration is discontinued.

Details of these techniques have been presented in the ANNUAL REPORT to the Committee in 1963 (Minutes of the 25th Meeting) by Deneau and Seevers (1963) and by Villarreal (1973).

SELF-ADMINISTRATION BY MONKEYS

Tests of self-administration determine the ability of the drug to maintain responding in monkeys trained to self-inject codeine. Each of at least three monkeys was studied with saline as a negative control and a number of doses of the test compound until a maximum rate of responding was obtained or until, in the absence of evidence of a reinforcing effect, directly observable changes in behavior were produced by the compound.

The schedule of intravenous drug delivery was a fixed-ratio 30; when a light above a lever was illuminated, the 30th response produced a five-second intravenous drug injection accompanied by another light that was illuminated during drug delivery. After each injection, a ten-minute timeout condition was in effect during which responses had no scheduled consequence and neither light was illuminated. Each of the two daily sessions consisted of 13 injections or 130 minutes, whichever occurred first. Other details of the procedure and initial findings with a variety of narcotics are given in previous reports (Woods, 1977; 1980).

Doses of the drugs are typically described in terms of moles/kg/injection (inj), to facilitate direct comparisons among drugs. Duplicate observations of codeine (7.5×10^{-7} mol/kg/inj; 0.32 mg/kg/inj) and of saline were obtained for each monkey. A saline substitution was conducted before and after the series of observations on a test drug; the control rates of codeine-reinforced responding were obtained by a random sampling of two sessions interpolated between the drug-substitution sessions. These data are represented in the following graphs with individual symbols for each of the monkeys; each symbol is the mean of duplicate observations for a given dose in each monkey. There are two additional types of averaged data presented. The closed circles indicate the averaged data for observations on the subset of monkeys used to study each drug under each of the experimental conditions. The open circles indicate the codeine and saline rates of responding of 20 monkeys studied under the same conditions. The brackets indicate ± 3 standard errors of the codeine mean, and + 3 standard errors of the saline mean for the group of 20 monkeys. In all cases, the rates of responding given are those calculated during only the fixed-ratio portion of each session.

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

Details of the binding assay were described in the 1978 ANNUAL REPORT (Swain et al., 1978). Briefly, aliquots of a membrane preparation from rat cerebrum were incubated with ^{3}H-etorphine in the absence and presence of 150 mM NaCl, and in the presence of different concentrations of the drug under investigation. ^{3}Stereospecific, i.e., opiate receptor related, interaction of ^{3}H-etor-

TABLE I

MOUSE ANALGESIA. Before submission to The University of Michigan, all compounds are evaluated for analgesic activity by Dr. Arthur E. Jacobson. Shown below are comparative data $\frac{(ED\ 50 mg/kg)}{mol/kg}$ (95% Confidence Interval) from Hot Plate[a-c] and Nilsen[d] assays.

Compound NIH #	HOT PLATE (sc/mg/kg) (sc, umol/kg)	HOT PLATE (oral,mg/kg) (oral, umol/kg)	NILSEN (sc, mg/kg) (sc. umol/kg)	NILSEN (oral, mg/kg) (oral, umol/kg)
Morphine sulfate NIH 0001, 9929	0.98 (0.83-1.1) 2.9 (2.5-3.3)	6.3 (4.7-8.3) 18.9 (14.1-24.9)	1.3 (1.0-1.7) 3.9 (3.0-5.1)	8.3 (6.0-11.4) 24.9 (18.0-34.1)
Codeine phosphate NIH 0002	6.8 (4.5-10.2) 17.1 (11.3-25.7)	13.5 (9.7-18.7) 34.0 (24.4-47.1)	7.4 (4.9-11.0) 18.6 (12.3-27.7)	14.7 (9.2-23.3) 37.0 (23.2-58.7)
Levorphanol tartrate NIH 4590	0.2 (0.1-0.3) 0.5 (0.2-0.7)	- -	0.2 (0.16-0.3) 0.5 (0.4-0.7)	2.5 (1.7-3.7) 6.2 (4.2-9.1)
Meperidine.HCl NIH 5221	5.3 (4.0-7.1) 18.7 (14.1-25.0)	- -	- -	- -
(-)-Metazocine.HBr NIH 7569	0.6 (0.5-0.9) 1.9 (1.4-2.8)	10.6 (8.0-14.1) 34.1 (25.7-45.3)	0.5 (0.3-0.7) 1.6 (1.0-2.3)	26.0 (21.0-33.0) 83.6 (67.5-106.1)

TABLE I Continued

Dihydromorphinone.HCl	0.19 (0.15-0.25)	0.9 (0.7-1.2)	0.2 (0.15-0.3)	1.8 (1.5-2.1)
NIH 0123	0.6 (0.5-0.8)	2.8 (2.2-3.7)	0.6 (0.5-0.9)	5.6 (4.7-6.5)
Nalorphine.HCl	9.9 (5.7-17.1)	-	23.0 (16.2-32.7)	-
NIH 2105	28.4 (16.4-49.1)	-	66.1 (46.6-94.0)	-
Cyclazocine	1.5 (1.1-2.1)	-	0.1 (0.07-0.16)	-
NIH 7981	5.5 (4.1-7.7)	-	0.4 (0.3-0.6)	-
Pentazocine	9.3 (6.7-12.8)	-	6.5 (4.4-8.8)	-
NIH 7958	32.6 (23.5-44.9)	-	22.8 (15.4-30.9)	-
Naltrexone.HCl	No dose response			
NIH 8503				
Naloxone.HCl	No dose response			
NIH 7890				

No antinociceptive activity in hot plate assay: Phenobarbital, amobarbital, diazepam, meprobamate, mescaline, oxazepam, flurazepam.

Chlorpromazine.HCl	1.1 (0.9-1.5)
	3.2 (2.4-4.2)

a) Eddy and Leimbach (1953); b) Jacobson and May (1965); c) Atwell and Jacobson (1978); d) Perrine, Atwell, Tice, Jacobson and May (1972).

phine was determined as the difference in binding obtained in the presence of an appropriate excess of dextrorphan and levorphanol, respectively. The potency of the drugs in inhibiting the stereospecific binding of ^{3}H-etorphine was determined from log-probit plots of the data. It should be noted that since April 1982 the concentration of ^{3}H-etorphine in the binding assay was reduced from 3.0 nM to 0.5 nM, a concentration approaching the K_D of the radiolabeled opiate. This change was implemented in order to let the determined EC50 approximate the true K_i of a given drug. However, due to the different concentration of the radiolabeled ligand, the EC50's determined since April, 1982 are lower than those obtained previously. For the purpose of reference, Table II contains EC50 values of representative opiates determined in binding assays using 0.5 nM ^{3}H-etorphine. Unless specifically noted in the Report, it should be assumed that 3.0 nM etorphine was used in the binding assays.

INHIBITION OF TWITCH IN ELECTRICALLY-DRIVEN GUINEA PIG ILEUM AND MOUSE VAS DEFERENS PREPARATIONS.

Submitted drugs are evaluated on two smooth muscle preparations, the details of which were described in the 1978 ANNUAL REPORT (Swain et al, 1978). Shown in the following pages are the EC50's for the tested drug alone, for the drug in the presence of naltrexone (a pure opioid antagonist which is more effective against so-called "mu" agonists than against so-called "kappa" agonists), and for the drug in the presence of UM 979 (an antagonist which appears to be more effective against "kappa" than against "mu" drugs) (Smith, 1978). The maximum depression of the electrically induced twitch in each of the preparations is also indicated. The concentrations of both naltrexone and UM 979 used in tests of antagonism are for the guinea pig ileum always 10^{-7} M, and for the mouse vas deferens always 10^{-8} M.

TABLE II

EC50 of representative opiates in displacing 0.5 nM ^{3}H-etorphine in a membrane preparation from rat cerebrum

Compound	EC50 (nM) -NaCl	EC50 (nM) +NaCl	+Na/-Na
UM 911	14.6	28.3	1.94
Morphine	14.0	23.6	1.69
Dextrorphan	6180	9820	1.59
UM 1071R	1.14	1.55	1.36
Ketazocine	10.7	14.1	1.32
Ethylketazocine	5.22	6.60	1.26
(-)SKF 10047	4.09	3.93	0.96
Etorphine	0.47	0.37	0.79
(-)Cyclazocine	0.85	0.53	0.63
Naltrexone	1.43	0.63	0.44

NOTE: Binding data for these and other compounds, determined in binding assays using 3.0 nM ^{3}H-etorphine, are included in the 1978 and 1981 ANNUAL REPORTS.

SUMMARY OF TESTS PERFORMED

The compounds which were evaluated at the University of Michigan during the past year and the individual tests which were performed are shown in Table III. Also shown are dates of Annual Reports in which results are reported of earlier tests on those compounds conducted at Michigan.

TABLE III

SUMMARY OF TESTS PERFORMED

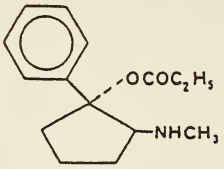
UM	NIH	CHEMICAL MCV	CLASS AND/OR GENERIC NAME	SDS	NW	N	SA	GPI	MVD	BIND	PDS
1216	9721	4186		-	-	-	+	+	+	+	-
1222	9742		1-allylpiperidine	-	-	-	-	+	+	+	-
1227	9739	4200	2-nitronaloxone	-	-	-	-	-	-	+	-
1232	9769		norketobemidone	-	-	-	-	+	+	1980	1980
1234	9651	4178		-	-	-	-	+	+	+	-
1236	9771	4205	methylpiperidine	-	-	-	-	+	+	-	-
1238	9791	4210	peptide	-	-	-	+	1981	1981	1981	-
1239	9788			-	-	-	+	-	-	-	-
1240	9787	4208	acetoxymorphinan	-	-	-	-	-	-	+	-
1241	9790	4209	norketobemidone	-	-	-	-	-	-	+	-
1244	9803	4211	noroxymorphone	+	+	-	-	+	+	+	-
1247	9806	4265	norketobemidone	+	+	-	-	+	+	+	-
1248	9807	4215	6,7-benzomorphan	-	-	-	-	+	+	+	-
1249	9808	4216	6,7-benzomorphan	-	-	-	-	+	+	+	-
1250	9809	4217	6,7-benzomorphan	-	+	-	-	+	+	+	-
1251	9810	4218		-	-	-	-	+	+	+	-
1256	9827	4223	Flurazepam	-	-	-	-	+	+	+	-

TABLE III Continued

UM	NIH	MCV	CHEMICAL CLASS AND/OR GENERIC NAME	SDS	NW	N	SA	GPI	MVD	BIND	PDS
1269	9614	4169	homobenzomorphan	-	-	-	+	1981	1981	1981	-
1275	9891	4246	n-propylmorphan	-	+	-	-	+	+	+	-
1278	9904	4252	benzazonine	+	-	-	-	+	+	+	-
1279	9897	4248	benzazonine	+	-	-	-	+	+	+	-
1282	9881	4239	morphan	-	-	-	-	+	+	+	-
1283	9882	4240	methylmorphan	-	-	-	-	+	+	+	-
1284	9883		morphan	-	-	-	-	+	+	+	-
1288	9889	4244	methylmorphan	-	-	-	-	+	+	+	-
1289	9890	4245	morphan	-	-	-	-	+	+	+	-
1290	9895	4235	benzazonine	-	-	-	-	+	+	+	-
1292	9899	4237	benzazonine	-	-	-	-	+	+	+	-
1293	9900	4238	benzazonine	-	-	-	-	+	+	+	-
1305	9450	4276	benzomorphan	+	+	-	-	-	-	-	-
1308	9905	4264	benzazonine	+	-	-	-	+	+	+	-
1309	9906	4265	benzazonine	+	-	-	-	+	+	+	-
1310	9926	4266	methoxymorphinan	+	+	-	-	-	-	-	-
1311	9929	4260	morphine	+	-	-	-	-	-	-	-
1312	9930	4261	naltrexone	+	+	-	-	-	-	-	-

TABLE III Continued

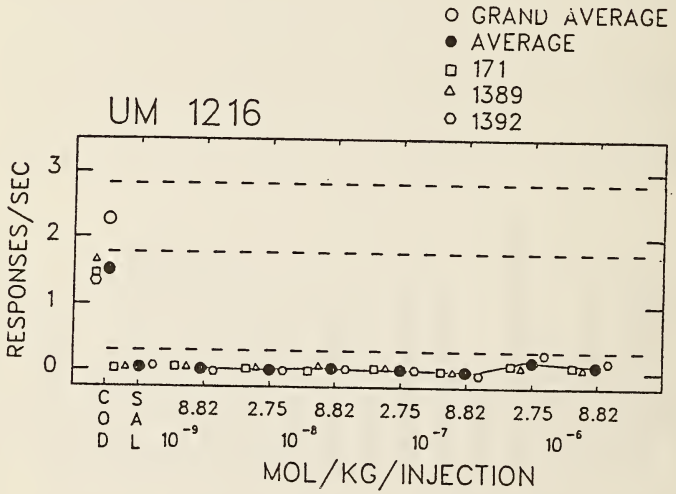
UM	NIH	MCV	CHEMICAL CLASS AND/OR GENERIC NAME	SDS	NW	N	SA	GPI	MVD	BIND	PDS
1313	9931	4280	methoxymorphinan	-	+	-	-	-	-	-	-
1314	9932	4281	methoxymorphinan	+	-	-	-	-	-	-	-
1315	9903	4254	benzazonine	-	-	-	-	+	+	+	-
1325	9508	4142	nordihydrocodeinone	-	-	-	+	-	-	-	-
1327	9945	4286	morphan	+	+	-	-	-	-	-	-
1330	9939	4270	propylmorphinan	-	-	-	-	+	+	+	-
1338	9957		methylmorphinan	-	-	-	-	+	+	+	-
1339	9958		methylmorphinan	-	-	-	-	+	+	+	-
1340	9959	4305	methylmorphinan	-	-	-	-	+	+	+	-
1344	9960		methylmorphinan	+	-	-	-	-	-	-	-
1347	9975	4296	methoxymorphinan	+	-	-	-	-	-	-	-
1381	10015	4317	dimethylmorphinan	+	-	-	-	+	+	+	-
1384	10017		dimethoxymorphinan	+	-	-	-	-	-	-	-
1385	10018		dimethoxymorphinan	+	+	-	-	-	-	-	-
1388	10021		morphan	+	-	-	-	-	-	-	-
1401	9615a	4176	benzazocine	-	-	-	-	-	-	+	



MOUSE ANALGESIA, ED50, (mg/kg)
Hot Plate: Incompletely active at 100

2-beta-Methylamino-1-phenylcyclopentanol propanoate ester, hydrogen maleate

DRUG SELF-ADMINISTRATION RHESUS MONKEYS



UM 1216 maintained, over a wide range of doses, rates of responding that were no different than those maintained by saline.

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

The EC50 of UM 1216 in displacing tritiated etorphine, in the presence and absence of NaCl, was higher than 20 uM.

INHIBITION OF TWITCH TO ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

In concentrations which ranged from 10^{-9}M to 3 x 10^{-4}M UM 1216 had no activity except for a slight decrease in the magnitude of the twitch at the highest concentration. Increases in baseline tension were observed at concentrations 3 x 20^{-6} M to 3 x 10^{-4} M Neither naltrexone nor UM 979 altered responses to UM 1216.

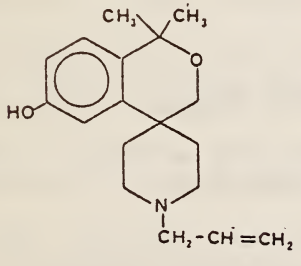
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

Concentrations between 10^{-9} M to 3 x 10^{-5} M UM 1216 had no effect. At concentrations between 3 x 10^{-5} M and 3 x 10^{-4} M, there was a marked increase in the magnitude of the twitch. This drug did not increase the baseline tension. UM 1216 did not directly contract the vas deferens. Naltrexone and UM 979 did not alter responses to this drug.

SUMMARY

UM 1216 appears to be devoid of morphine-like activity. It has a very low potency in displacing tritiated etorphine. Its actions upon the two smooth muscle preparations resemble those of the withdrawal-inducing benzazocines, UM 1037 and UM 1046.

UM 1222 NIH 9742



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 30% @ 20, 60% @ 50

Spiro[(1,1-dimethyl-3-ethyl-7-hydroxy-1H-2-benzopyran)-4,4'-(1-allylpiperidine)] hydrobromide

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

The EC50 of UM 1222 in displacing tritiated etorphine, in the presence and absence of NaCl, was higher than 20 uM.

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

At concentrations which ranged from 10^{-9}M to 10^{-4}M this drug did not inhibit the twitch except at highest concentrations (3 x 10^{-5} M) and 10^{-4} M). The maximum inhibition ranged between 15 and 42%. EC50's could not be determined.

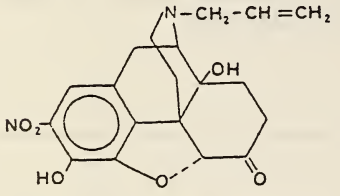
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

At none of the concentrations studied (10^{-9} to 10^{-4}M) did this drug decrease the twitch. High concentrations (3 x 10^{-5} and 10^{-4} M) caused a two-fold increase in the magnitude of the twitch. Neither naltrexone nor UM 979 altered responses to UM 1222.

SUMMARY

UM 1222 is devoid of opiate activity in the binding assay and upon the guinea pig ileum and mouse vas deferens.

UM 1227 NIH 9739 MCV 4200



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 3.5 (2.8-4.3)
Nilsen: 6.0 (4.5-8.0)

2-Nitronaloxone

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

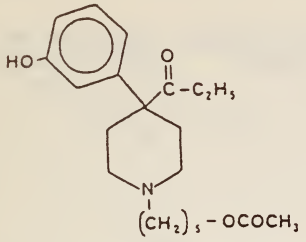
The EC50 of UM 1227 in displacing tritiated etorphine, in the presence or absence of NaCl, was higher than 20 uM.

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

At concentrations used for this preparation the compound was not soluble.

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

At concentrations used for this preparation the compound was not soluble.



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 23.6 (17.7-31.5)

N-Pentylacetate-N-norketobemidone

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 2200 nM in absence of NaCl
EC50 of 1957 nM in presence of NaCl
Sodium ratio = 0.89

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC50	Maximum Response (%)
Drug Alone	2.29×10^{-6} M	43.6
After naltrexone		no response
After UM 979		no response

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

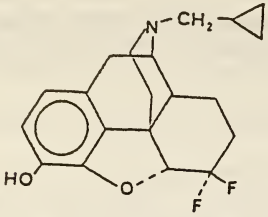
UM 1232 did not decrease the magnitude of the twitch, but caused large increases in the magnitude of the twitch at the highest concentrations studied.

OBSERVATIONS IN MORPHINE-DEPENDENT MONKEYS

UM 1232 increased the severity of morphine withdrawal in the morphine-dependent monkey but was not very potent in doing so.

SUMMARY

UM 1232 appears to have some morphine-like activity upon the guinea pig ileal preparation although it is about 100-fold less potent and about two-thirds as efficacious as morphine. It is devoid of opiate activity on the mouse vas deferens.



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 17.2 (7.3-40.4)

N-Cyclopropylmethyl-6,6-difluorodihydromorphine hydrochloride

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 0.54 nM in absence of NaCl
EC50 of 0.31 nM in presence of NaCl
Sodium ratio = 0.57

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

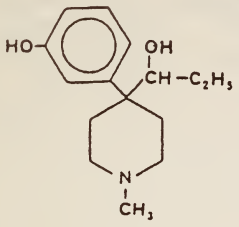
	EC50	Maximum Response (%)
Drug alone	6.05×10^{-9} M	66.1
After naltrexone	9.79×10^{-9} M	65.9
After UM 979	7.36×10^{-9} M	62.8

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

Only at the highest concentration (10^{-4} M) did UM 1234 inhibit the twitch. Neither naltrexone or UM 979 affected this inhibitory effect of UM 1234. Concentrations between 3×10^{-6} and 10^{-4} M caused large increases in the magnitude of the twitch.

SUMMARY

UM 1234 has a high affinity in the opiate receptor binding assay with a sodium response ratio that suggests antagonist activity. Its inhibitory actions on the smooth muscle preparations were not reversed by narcotic antagonist nor were the increases in twitch height produced at higher concentrations altered by narcotic antagonist. Thus, this compound may have antagonist actions in vivo at low doses and non-narcotic actions at much higher doses.



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 0% @ 20, 80% @ 50, 40% @ 100

4-(1-Hydroxypropyl)-4-m-hydroxyphenyl-1-methylpiperidine

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

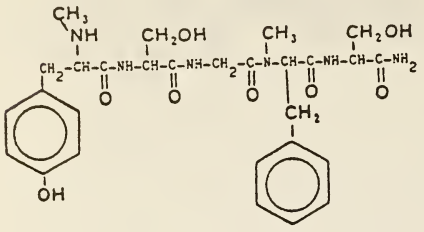
	EC50	Maximum Response (%)
Drug alone	3.44×10^{-6} M	91.5
After naltrexone	9.53×10^{-6} M	unchanged
After UM 979	6.32×10^{-6} M	unchanged

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response (%)
Drug alone	7.52×10^{-7} M	83.0
After naltrexone	2.62×10^{-6} M	unchanged
After UM 979	6.71×10^{-6} M	unchanged

SUMMARY

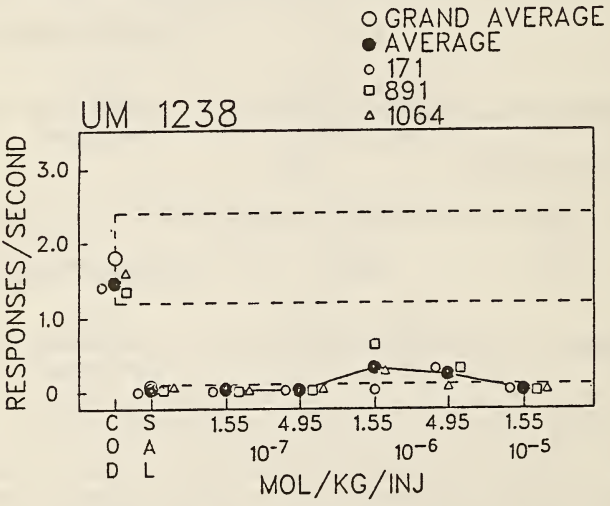
On both smooth muscle preparations UM 1236 had effects similar to morphine which were antagonized slightly by naltrexone, but not by UM 979. It was considerably less potent than morphine on both preparations.



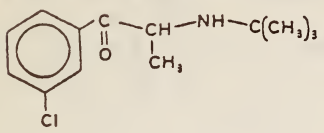
MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 1.4 (1.1-1.8)
Nilsen: 1.5 (1.1-2.1)

N-Methyl-L-tyrosyl-D-serylglycyl-N-methyl-L-phenylalanyl-D-serinamide monoacetate

DRUG-SELF ADMINISTRATION IN RHESUS MONKEYS



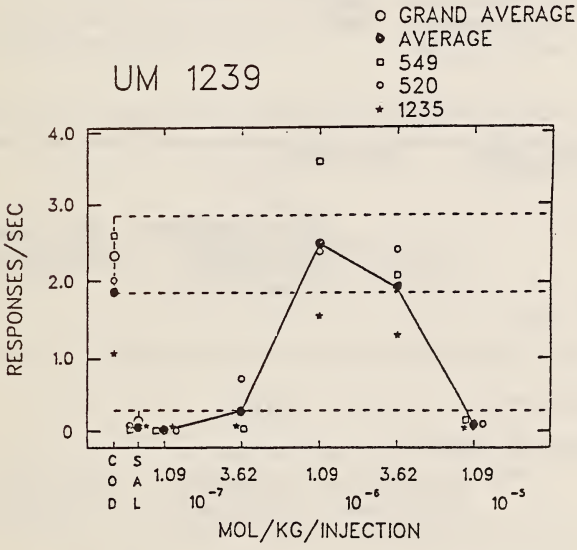
At doses of 1.55×10^{-6} and 4.95×10^{-6}, rates of responding were slightly higher than those maintained by saline. At doses of 1.55×10^{-7}, 4.95×10^{-7} and 1.55×10^{-5} rates were no higher than those maintained by saline.



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: Incompletely active at 100 mg/kg
Nilsen: 25.8 (17.4-38.5)

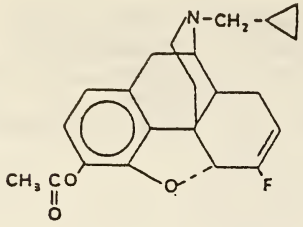
1-(3-Chlorophenyl)2-(1,1-dimethylamino)propan-1-one

DRUG SELF-ADMINISTRATION IN RHESUS MONKEYS



UM 1239 maintained rates higher than the average codeine rates in all 3 monkeys tested (134% of the codeine rate). 3.62×10^{-6} mol/kg (3.0 mg/kg) maintained an average rate 102% of that maintained by codeine. Lower and higher UM 1239 injection doses maintained rates not higher than those maintained by saline. Like other stimulants of the amphetamine-like substituted phenylethylamine class and cocaine, this drug produced high rates of drug-maintained responding.

UM 1240 NIH 9787 MCV 4208



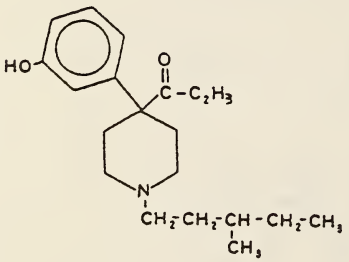
MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 20% @ 20, 0% @ 50, 40% @ 100
Nilsen: 0% @ 5, 25% @ 10 & 40, 50% @ 20

17-Cyclopropylmethyl-6,7-dehydro-4,5-alpha-epoxy-6-fluoro-3-acetoxymorphinan

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 3.92 nM in absence of NaCl
EC50 of 2.29 nM in presence of NaCl
Sodium response ratio = 0.58

UM 1241 NIH 9790 MCV 4209

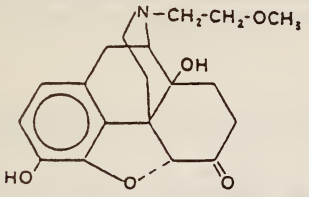


MOUSE ANALGESIA, ED50, (mg/kg)
Hot Plate: 16.6 (12.5-22.1)
Nilsen:

3-Methylpentyl-N-norketobemidone hydrobromide

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 515 mM in absence of NaCl
EC50 of 515 mM in presence of NaCl
Sodium response ratio = 1.00



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 7.7 (5.9-10.0)
Nilsen: 20.1 (15.9-25.4)

(-)-N-(2-Methoxyethyl)noroxymorphone hydrochloride

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 4.97 nM in absence of NaCl
EC50 of 2.99 nM in presence of NaCl
Sodium response ratio = 0.60

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC50	Maximum Response (%)
Drug alone	1.5×10^{-9} M	33.4
After naltrexone	Completely antagonized	
After UM 979	Completely antagonized	

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response (%)
Drug alone	7.13×10^{-6} M	37.0
After naltrexone	Completely antagonized	
After UM 979	Completely antagonized	

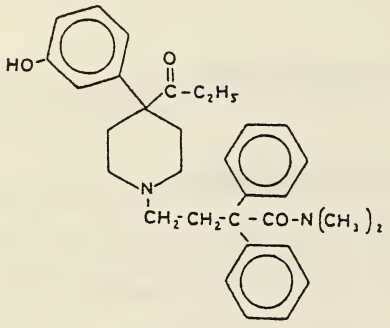
OBSERVATIONS IN MORPHINE-DEPENDENT RHESUS MONKEYS

UM 1244 precipitated signs of narcotic withdrawal in the morphine-dependent monkey. The signs were elicited promptly and at higher doses were long lasting. UM 1244 is about 6 to 10 times as potent as nalorphine and comparable to naloxone or naltrexone.

SUMMARY

The compound possesses both narcotic agonist and antagonist actions with the latter occurring at quite low doses. It may also be a partial agonist in both smooth muscle preparations.

UM 1247 NIH 9806 MCV 4214



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 20.5 (13.6-30.9)

N-[3-(N,N-Dimethylcarbamoyl)-3,3-diphenylpropyl]-norketobemidone hydrochloride

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 85.9 nM in absence of NaCl
EC50 of 94.8 nM in presence of NaCl
Sodium response ratio = 1.10

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC50	Maximum Response (%)
Drug alone	1.16×10^{-7} M	53.7
After naltrexone	Completely antagonized	
After UM 979	2.11×10^{-6} M	33.1

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response (%)
Drug alone	4.29×10^{-8} M	91.3
After naltrexone	2.24×10^{-7} M	58.4
After UM 979	1.95×10^{-7} M	Unchanged

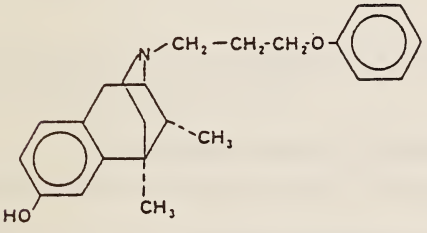
OBSERVATIONS IN THE MORPHINE-DEPENDENT RHESUS MONKEYS

At doses of 3 to 10 mg/kg, UM 1247 was without effect but abscesses at injection sites that did not occur after vehicle alone suggest that the drug may not have been absorbed.

SUMMARY

The effects of UM 1247 in the binding assay and the mouse vas deferens agree and suggest a potency comparable to morphine. However, its lack of action in the dependent rhesus monkey at 3 to 10 mg/kg doses; (doses that should be active based on the in vitro potency) suggests that the compound may be poorly absorbed when administered subcutaneously. It has morphine-like activity on the mouse vas deferens and the guinea pig ileum preparations. It is unusual that upon both preparations, naltrexone reduces or abolishes responses to UM 1247. On the guinea pig ileum UM 979 also reduces the maximum response to UM 1247 but on the mouse vas deferens it seems to act as if it were a competitive antagonist of UM 1247.

UM 1248 NIH 9807 MCV 4215



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 0.33 (0.24-0.44)

(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(3-phenoxypropyl)-6,7-benzomorphan hydrochloride

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 29.6 nM in absence of NaCl
EC50 of 90.6 nM in presence of NaCl
Sodium response ratio = 3.06

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC50	Maximum Response (%)
Drug alone	1.40×10^{-6} M	67.5
After naltrexone	3.22×10^{-5} M	unchanged
After UM 979	1.42×10^{-4} M	unchanged

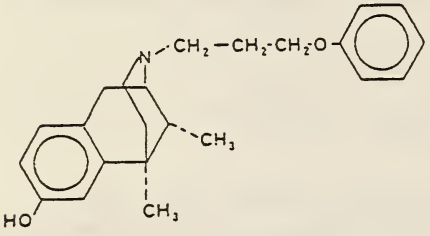
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response (%)
Drug alone	6.11×10^{-7} M	99.5
After naltrexone	1.97×10^{-6} M	unchanged
After UM 979	1.50×10^{-6} M	unchanged

SUMMARY

See UM 1249.

UM 1249 NIH 9808 MCV 4216



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 8.7 (6.3-12.1)
Nilsen: 11.7 (8.0-17.3)

(+)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(3-phenoxypropyl)-6,7-benzomorphan hydrochloride

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

UM 1249 failed to displace tritiated etorphine in presence or absence of NaCl up to concentration of 2 uM.

INHIBITION OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

No response until a concentration of 10^{-5} M. Maximum response was 33-59% inhibition of the twitch. Concentrations of 10^{-4} M caused spontaneous activity of the preparation and an increase in baseline tension. Therefore, EC50 could not be calculated. Neither naltrexone nor UM 979 altered responses to UM 1249.

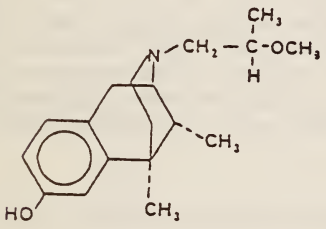
INHIBITION OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

At no concentration did UM 1249 inhibit the twitch. At concentrations of 3×10^{-6} M and higher there was an increase in the magnitude of the twitch. The maximum increase was approximately two-fold and occurred at a concentration of 10^{-5} M. Neither naltrexone nor UM 979 altered responses to UM 1249.

SUMMARY

In the binding assay UM 1248 was twice as potent as morphine in the absence of sodium chloride. On both the mouse vas deferens and guinea pig ileum preparations, UM 1248 appears to be morphine-like in its activity. It is about one-tenth the potency of morphine on the mouse vas deferens preparation and one-hundredth the potency of morphine on the guinea pig ileum. UM 1249, the (+)-isomer of UM 1248, is devoid of significant opiate activity on these preparations although it produces analgesia with low potency.

UM 1250 NIH 9809 MCV 4217



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 0.008
(0.006-0.01)

(-)-[(1R,5R,2''S)-5,9-Dimethyl-2'-hydroxy-2-(2-methoxypropyl)-6,7-benzomorphan hydrobromide

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 7.1 nM in absence of NaCl
EC50 of 15.1 nM in presence of NaCl
Sodium response ratio = 2.14

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC50	Maximum Response (%)
Drug alone	3.18×10^{-10} M	60.9
After naltrexone	7.99×10^{-8} M	63.7
After UM 979	2.96×10^{-9} M	52.8

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response (%)
Drug alone	2.44×10^{-9} M	100
After naltrexone	4.75×10^{-9} M	99.4
After UM 979	4.14×10^{-9} M	100

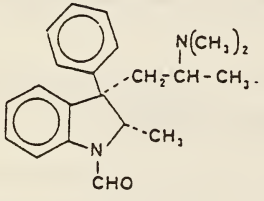
OBSERVATIONS IN MORPHINE-DEPENDENT RHESUS MONKEYS

UM 1250 produced sedation, ptosis, mydriasis, and ataxia at low doses (0.003 to 0.03 mg/kg). At doses of 0.0056 and 0.01 mg/kg the drug also reversed withdrawal signs; however, complete reversal of withdrawal was not obtained since marked sedation at higher doses precluded the grading of withdrawal. The sedative effects of the drug resembled those seen with ethylketazocine.

SUMMARY

Upon the guinea pig ileum UM 1250 appears to be morphine-like in that it is antagonized by both naltrexone and UM 979. In contrast, on the mouse vas deferens, although UM 1250 is 10 times more potent than morphine, it does not appear to be morphine-like since neither naltrexone nor UM 979 caused large shifts to the right in the concentration effect curve for UM 1250. The size of the sodium response ratio obtained from the binding assay is consistent with the agonist actions of the compound and the compound was consistently more potent than morphine in each of the preparations. The observations in morphine-dependent rhesus monkeys suggest that UM 1250 may have mixed morphine-like and ethylketazocine-like effects.

UM 1251 NIH 9810 MCV 4218



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 40% @ 20 & 50, 50% @ 100
Nilsen: 28.9 (18.9-44.3)

2,3-Dihydro-2-methyl-3-[2-(dimethylamino)propyl]-3-phenyl-1H-indol-1-carboxaldehyde methanesulfonate

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

UM 1251 failed to displace tritiated etorphine in the presence or absence of NaCl up to concentrations of 10 uM.

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC50	Maximum Response (%)
Drug alone	6.69×10^{-7} M	92.9
After naltrexone	8.67×10^{-7} M	93.9
After 979	7.24×10^{-7} M	91.0

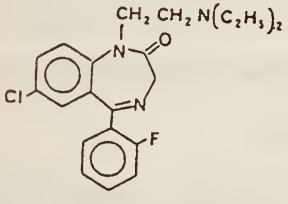
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

UM 1251 did not inhibit the twitch of this preparation at any concentration until 10^{-4} M at which there was a 100% inhibition of the twitch. Neither naltrexone nor UM 979 has any effect upon this response to UM 1251.

SUMMARY

UM 1251 is devoid of morphine-like activity.

UM 1256 NIH 9827 MCV 4223



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 0% @ 20 & 100,
10% @ 50

Flurazepam hydrochloride

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

UM 1256 failed to displace significantly tritiated etorphine in the presence or absence of NaCl up to concentrations of 20 uM.

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC50	Maximum Response (%)
Drug alone	1.57×10^{-5} M	94.3
After naltrexone	3.26×10^{-5} M	95.2
After UM 979	3.06×10^{-5} M	94.2

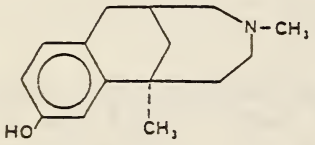
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response (%)
Drug alone	1.73×10^{-9} M	59.8
After naltrexone	1.01×10^{-9} M	78.1
After UM 979	7.84×10^{-10} M	48.3

SUMMARY

UM 1256 has two inhibitory effects upon the guinea pig ileal preparation. At low concentrations it causes a slight inhibition. At higher concentrations it causes a further inhibition. This latter inhibition of the twitch is antagonized slightly by both naltrexone and UM 979. On the mouse vas deferens, UM 1256 is devoid of opiate-like activity.

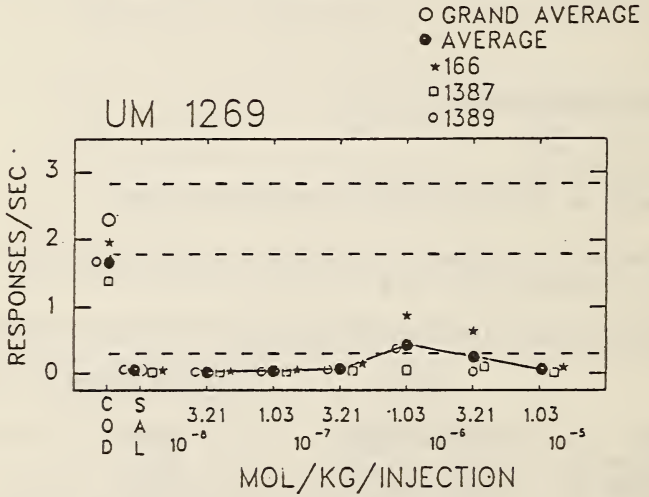
UM 1269 NIH 9614 MCV 4169



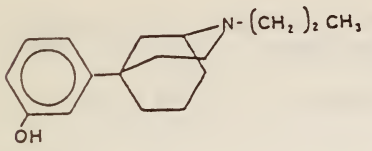
MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 2.5 (1.9-3.3)
Nilsen: 13.0 (9.6-17.7)

(-)-9-Hydroxy-4,7-dimethyl-C-homobenzomorphan hydrobromide

DRUG SELF-INJECTION IN THE RHESUS MONKEY



UM 1269 maintained self-injection rates of responding slightly above those of saline only at a dose of 1.03×10^{-6} Mol/kg/inj (0.3 mg/kg/inj). In only one of the three monkeys did UM 1269 maintain rates of responding higher than those of saline. The maximum percent of the codeine response rates was 26 at 1.03×10^{-6} mol/kg/inj. A single observation was made at 3.21×10^{-5} mol/kg/inj. Following a single injection (10 mg/kg) the monkey was sedated and ataxic. Following a second injection, he became unresponsive. Naltrexone (0.32 mg/kg) did not alter the effect.



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 9.2 (6.4-13.0)

(+)-5-(m-Hydroxyphenyl)2-n-propylmorphan hydrochloride

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 1970 nM in absence of NaCl
EC50 of 1760 nM in presence of NaCl
Sodium response ratio = 0.89

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC50	Maximum Response (%)
Drug alone	2.16×10^{-5} M	89.8
After naltrexone	7.64×10^{-5} M	92.2
After UM 979	1.56×10^{-4} M	85.3

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

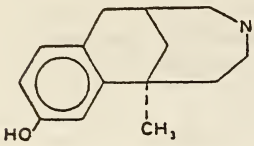
At no concentration did UM 1275 inhibit the twitch of this preparation. At concentrations of 3×10^{-6} M and higher there were increases in the magnitude of the twitch. The maximum increase was 1.5-fold and occurred at a concentration of 3×10^{-5}M. Neither naltrexone nor UM 979 altered this response to UM 1275.

OBSERVATIONS IN MORPHINE-DEPENDENT RHESUS MONKEYS

UM 1275 failed to produce any effects over a range of doses from 1 to 5.6 mg/kg.

SUMMARY

UM 1275 might have some morphine-like activity upon the guinea pig ileum preparation. Upon the ileum it is approximately 1000-fold less potent than morphine although it is more efficacious in suppressing the twitch. Both naltrexone and UM 979 slightly antagonized responses to UM 1275. On the mouse vas deferens UM 1275 is devoid of morphine-like activity. Over the dose range studied, UM 1275 was inactive in the morphine-dependent monkey; however, the compound should be studied *in vivo* at higher doses based on the *in vitro* findings.



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 20% @ 20, 30% @ 50
Nilsen: 25% @ 50

(-)-1-Methyl-4-isopentenyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

UM 1278 failed to displace tritiated etorphine significantly either in the presence or the absence of NaCl up to concentrations of 10 uM.

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

At no concentration did UM 1278 inhibit the twitch of this preparation. At concentrations of 10^{-5} M and higher UM 1278 caused marked increases in the baseline tension of the preparation. Neither naltrexone nor UM 979 altered responses to this compound.

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

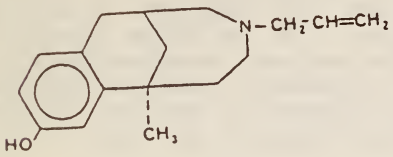
At no concentration did UM 1278 inhibit the twitch of this preparation. At concentrations of 10^{-6} M and greater UM 1278 increased the magnitude of the twitch with the maximum response being a two-fold increase which occurred at a concentration of 10^{-4} M. Neither naltrexone nor UM 979 altered responses of the preparation to UM 1278.

OBSERVATIONS IN MORPHINE-DEPENDENT RHESUS MONKEYS

There was a slight exacerbation of withdrawal signs at the 10 mg/kg dose.

SUMMARY

Upon both the mouse vas deferens and guinea pig ileal preparations UM 1278 is devoid of morphine-like activity. There was an indication that withdrawal severity was enhanced by UM 1278. This general pattern of pharmacological effects resembles that of other compounds evaluated previously (UM 1037 and UM 1046). See also the racemate (UM 1308) and (+)-isomer (UM 1315) of this compound.



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	80% @ 20 (50% convulse), 40% @ 10
Nilsen:	inactive @ 5

±-1-Methyl-4-allyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 6010 nM in the absence of NaCl
EC50 of 9810 nM in the presence of NaCl
Sodium response ratio = 1.63

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

At no concentration did UM 1279 inhibit the twitch of this preparation. At high concentrations UM 1279 caused increases in the baseline tension. Neither naltrexone nor UM 979 altered responses of this preparation to UM 1279.

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

Only at a concentration of 10^{-6} M did UM 1279 inhibit the twitch of this preparation. Higher concentrations increased the magnitude of the twitch. The maximum response was a 2-fold increase in twitch height which occurred at a concentration of 10^{-4} M. Neither naltrexone nor UM 979 altered responses of this preparation to UM 1279.

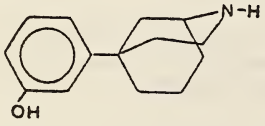
OBSERVATIONS IN NORMAL AND MORPHINE-DEPENDENT RHESUS MONKEYS

UM 1279 produced a set of behavioral signs of ataxia, unresponsiveness, incoordination, increased pupil size, and increased respiration in both normal and morphine-dependent monkeys. These signs resemble those of phencyclidine. UM 1279 was slightly less potent than phencyclidine in producing these effects.

SUMMARY

UM 1279 was devoid of morphine-like activity upon both smooth muscle preparations, and at high concentrations the compound resembled UM 1046 and UM 1037. UM 1279 displaced tritiatated etorphine only at high concentrations. In the rhesus monkey, UM 1279 resembled phencyclidine. This compound resembles UM 1267, 1268, 1269, 1277, 1280 and 1281 in producing phencyclidine-like actions while having little, if any, affinity in the opiate binding assay. See also the (+)-isomer of this compound (Um 1290).

UM 1282 NIH 9881 MCV 4239



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 0% @ 20, 30% @ 50, 10% @ 100

(-)-5-(m-Hydroxyphenyl)morphan hydrochloride

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 3360 nM in the absence of NaCl
EC50 of 1810 nM in the presence of NaCl
Sodium response ratio = 0.53

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

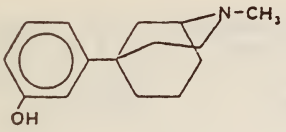
	EC50	Maximum Response (%)
Drug alone	9.50×10^{-9} M	15.3
After naltrexone	abolished response	
After UM 979	abolished response	

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

UM 1282 was devoid of activity except at concentrations of 10^{-4} M and higher at which it caused a marked suppression of the twitch.

SUMMARY

UM 1282 may have antagonist properties as suggested by its low sodium ratio. The drug might also have a very slight morphine-like effect upon the guinea pig ileum which is completely blocked by both antagonists. In the mouse vas deferens, it appears to be devoid of morphine-like activity and only at very high doses does it suppress the twitch.



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 2.0 (1.4-2.8)

(-)-5-(m-Hydroxyphenyl)-2-methylmorphan hydrochloride

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 487 nM in absence of NaCl
EC50 of 443 nM in presence of NaCl
Sodium response ratio =0.94

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

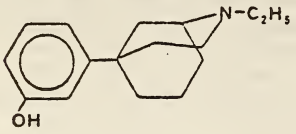
	EC50	Maximum Response (%)
Drug alone	4.49×10^{-9} M	31.3
After naltrexone	complete antagonism	
After UM 979	complete antagonism	

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response (%)
Drug alone	1.28×10^{-6} M	62.6
After naltrexone	2.09×10^{-6} M	42.8
After UM 979	1.50×10^{-6} M	54.8

SUMMARY

UM 1283 displaced etorphine with lower potency than morphine with an intermediate value of the sodium response ratio. The potency estimates are not closely matched between the binding and either of the smooth muscle preparations. UM 1283 might have slight morphine-like activity on the guinea pig ileum which is completely blocked by both antagonists. On the mouse vas deferens, UM 1283 is an agonist of low potency and the effect of the antagonist is somewhat unusual in that naltrexone alone decreases the magnitude of the maximum response without changing the EC50 for UM 1283. The (+)-isomer of this compound has greater narcotic activity (see UM 1288).



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 50% @ 20, 60% @ 50 (toxic @ 100)
Nilsen: 12% @ 50

(-)-2-Ethyl-5-(m-hydroxyphenyl)morphan hydrochloride

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 3650 nM in absence of NaCl
EC50 of 1780 nM in the presence of NaCl
Sodium response ratio = 0.49

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

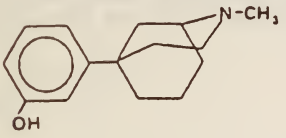
	EC50	Maximum Response (%)
Drug alone	1.53×10^{-7} M	44.3
After naltrexone		unchanged
After UM 979		unchanged

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

At no concentration did UM 1284 suppress the twitch of this preparation, although at concentrations of 10^{-5} and higher there were increases in the magnitude of the elicited twitch. Neither naltrexone nor UM 979 altered the response of this compound.

SUMMARY

See UM 1289.



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 0.63 (0.53-0.75)

(+)-5-(m-Hydroxyphenyl)-2-methylmorphan hydrochloride

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING (0.5 nM)

EC50 of 56.6 nM in absence of NaCl
EC50 of 85.7 nM in presence of NaCl
Sodium response ratio = 1.51

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

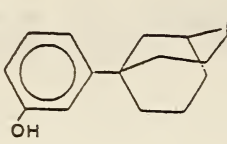
	EC50	Maximum Response (%)
Drug alone	1.81×10^{-7} M	94.6
After naltrexone	1.23×10^{-5} M	78.7
After UM 979	4.31×10^{-6} M	86.9

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response (%)
Drug alone	9.96×10^{-7} M	100
After naltrexone	2.60×10^{-6} M	88.1
After UM 979	2.67×10^{-6} M	91.8

SUMMARY

Upon each of the preparations UM 1288 resembled morphine but was somewhat less potent. See the (-)-isomer of this compound (UM 1283).



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 15.8 (12.1-20.5)

(+)-2-Ethyl-5-(m-hydroxyphenyl)morphan hydrochloride

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING (0.5 nM)

EC50 of 1462 nM in absence of NaCl
EC50 of 1593 nM in presence of NaCl
Sodium response ratio = 1.09

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

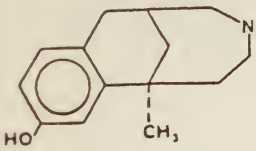
	EC50	Maximum Response (%)
Drug alone	1.86×10^{-5} M	91.5
After naltrexone	2.07×10^{-5} M	85.2
After UM 979	9.67×10^{-6} M	80.9

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response (%)
Drug alone	1.01×10^{-6} M	48.6
After naltrexone	2.89×10^{-6} M	39.2
After UM 979	1.39×10^{-6} M	32.8

SUMMARY

In the binding assay, both isomers (UM 1284 and UM 1289) have very low potency. Additionally, they fail to have opiate-like agonist activity upon either smooth muscle preparation.



MOUSE ANALGESIA, ED50 (mg/kg)
Hot plate: 90% @ 5, 20% @ 2, 0% @ 1 (90% convulsed @ 2)

Nilsen: 0% @ 5 & 1

(+)-4-Allyl-10-hydroxy-1-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4- benzazonine

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING (0.5 nM)

EC50 of 845 in absence of NaCl
EC50 of 1348 in presence of NaCl
Sodium response ratio = 1.59

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC50	Maximum Response (%)
Drug alone	7.42×10^{-7} M	42.3
After naltrexone		slight decrease
After UM 979		no decrease

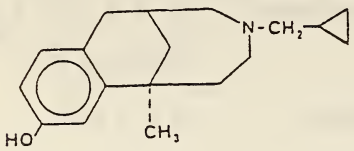
Both naltrexone and UM 979 markedly inhibited the response to UM 1290. At concentrations of 1×10^{-6} M and higher, in the presence of naltrexone, the magnitude of the twitch was increased. At concentrations of 10^{-6} M and higher, in the presence of UM 979, the magnitude of the twitch increased.

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response (%)
Drug alone	1.81×10^{-7} M	69.8
After naltrexone	6.60×10^{-8} M	64.5
After UM 979	1.02×10^{-7} M	74.7

SUMMARY

Upon the guinea pig ileum, UM 1290 appears to have some opiate-like actions although these are not pronounced. Upon the mouse vas deferens, UM 1290 appears to be devoid of opiate-like activity. See also the racemate (UM 1279).



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 30% @ 20, 50% @ 5
Nilsen: 0% @ 5 & 1

(+)-4-Cyclopropylmethyl-10-hydroxy-1-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING (0.5 nM)

EC50 of 1223 in the absence of NaCl
EC50 of 1463 in the presence of NaCl
Sodium response ratio = 1.20

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

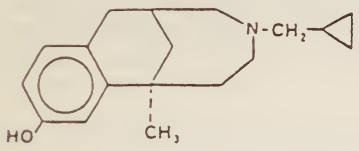
	EC50	Maximum Response (%)
Drug alone	1.16×10^{-5} M	39.6
After naltrexone	markedly antagonized	
After UM 979	markedly antagonized	

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

Only at a concentration of 3×10^{-6} M did UM 1292 produce a slight decrease in the magnitude of the twitch (less than 10%). At concentrations of 10^{-5} M and higher UM 1292 increased the magnitude of the twitch. This increase was twice the baseline at a concentration of 10^{-4} M. Neither naltrexone nor UM 979 altered responses of this preparation to UM 1292.

SUMMARY

UM 1292 may have slight opiate-like activity at high concentrations on the guinea pig ileum; however, on the mouse vas deferens preparation this drug seems to be completely devoid of opiate activity. See also UM 1293, the (-)-isomer.



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 10% @ 20, 20% @ 50
Nilsen: 0% @ 20, 25% @ 50

(-)-4-Cyclopropylmethyl-10-hydroxy-1-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

The EC50 of UM 1293 in displacing tritiated etorphine (0.5 nM) in the absence or presence of NaCl was higher than 6 uM.

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

At no concentration did UM 1293 decrease the magnitude of the twitch of this preparation. At concentrations of 10^{-6} M and greater this drug increased the magnitude of the twitch, and at a concentration of 10^{-5} M and greater UM 1293 caused a baseline contraction. Neither naltrexone nor UM 979 altered responses of UM 1293 on this preparation.

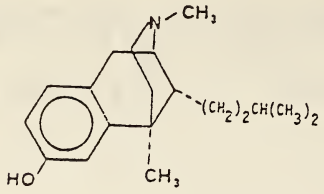
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

UM 1293 did not inhibit the twitch of this preparation at any concentration studied.

SUMMARY

UM 1293 does not have opiate activity. See the (+)-isomer (UM 1292).

UM 1305 NIH 9450 MCV 4276



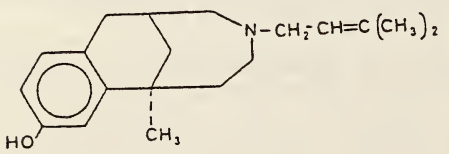
MOUSE ANALGESIA, ED50 (mg/kg)
Hot plate: 14.1 (11.7-17.0)
Nilsen: 19.7 (13.4-29.0)

2,5-Dimethyl-2'-hydroxy-9 alpha-isopentyl-6,7-benzomorphan methanesulfonate

OBSERVATIONS IN NORMAL AND MORPHINE-DEPENDENT RHESUS MONKEYS

Doses of 5.6, 10.0 and 17.0 mg/kg were tested in withdrawn and non-withdrawn subjects. At the lower doses there were no clear effects. The highest dose was preconvulsive. In normal subjects 10.0 mg/kg produced pupil dilation, tremor, some ataxia, and convulsions in one monkey. The effects in the monkey that did not convulse were not reversed by naloxone. In normal subjects 5.6 mg/kg did not reverse effects of 10.0 mg/kg morphine.

UM 1308 NIH 9905 MCV 4264



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 20% @ 20, 70% @ 50

±-1-Methyl-4-isopentenyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING (0.5 nM)

EC50 of 793 in absence of NaCl
EC50 of 1315 in presence of NaCl
Sodium response ratio = 1.66

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

In control experiments, UM 1308 caused very slight inhibition of the twitch (less than 10%) at a concentration of 10^{-5} M. Higher concentrations caused increases in the magnitude of the twitch and a baseline contraction at a concentration of 10^{-4} M. The slight inhibitory effect of UM 1308 was completely antagonized by both naltrexone and UM 979.

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

In control experiments, UM 1308 caused very slight inhibition of the twitch (less than 15%) at a concentration of 3×10^{-6} M. Higher concentrations increased the magnitude of the twitch. Both naltrexone and UM 979 antagonized this slight inhibitory effect.

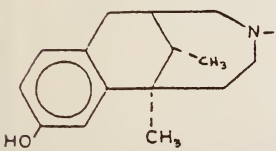
OBSERVATIONS IN NORMAL AND MORPHINE-DEPENDENT MONKEYS

UM 1308 failed to suppress withdrawal at 1 to 5.6 mg/kg. At 10 mg/kg it appeared to increase signs of withdrawal; however, at this dose it produced convulsions in nonwithdrawn rhesus monkeys. In normal monkeys UM 1308 failed to antagonize effects of 10.0 mg/kg morphine.

SUMMARY

It is unlikely that the slight exacerbation of withdrawal signs at 10 mg/kg was mediated by narcotic mechanisms, due to the lack of narcotic activity upon any of the in vitro preparations. On the smooth muscle preparations it resembles UM 1046 and 1037. See also the isomers of this compound (UM 1278 and UM 1315).

UM 1309 NIH 9906 MCV 4265



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 11.5 (8.9-15.0)

1,12 alpha-Dimethyl-4-isopentenyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING (0.5 nM)

EC50 of 364 nM in absence of NaCl
EC50 of 611 nM in presence of NaCl
Sodium response ratio = 1.68

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC50	Maximum Response (%)
Drug alone	2.20×10^{-6} M	63.3
After naltrexone	2.50×10^{-6} M	23.2
After UM 979	2.80×10^{-6} M	31.7

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

At no concentration did UM 1309 decrease the magnitude of the twitch. At high concentrations this drug increased the magnitude of the twitch.

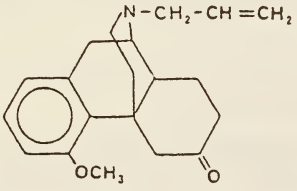
OBSERVATIONS IN MORPHINE-DEPENDENT RHESUS MONKEYS

UM 1309 suppressed the withdrawal syndrome produced by morphine deprivation. Due to the small amount of the drug supplied, its potency could not be estimated.

SUMMARY

The binding assay and the observations in dependent monkeys suggest that this compound has morphine-like agonist actions. The smooth muscle preparations suggest a different mode of action in these preparations.

UM 1310 NIH 9926 MCV 4266,4279



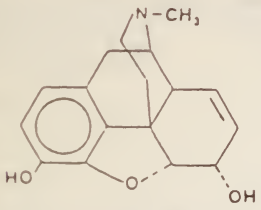
MOUSE ANALGESIA, ED50 (mg/kg)
HOT PLATE: 20% @ 20, 30% @ 50

(-)-N-Allyl-4-methoxymorphinan-6-one

OBSERVATIONS OF MORPHINE-DEPENDENT RHESUS MONKEYS

UM 1310 precipitated withdrawal with a potency of one-thirtieth to one-one hundredth that of naloxone.

UM 1311, 114 NIH 9929,0001 MCV 4260



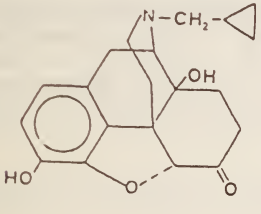
MOUSE ANAIGESIA, ED50 (mg/kg)
Hot Plate: 0.87 (0.63-1.2)
Nilsen: 1.3 (0.97-1.9)

Morphine

OBSERVATIONS OF MORPHINE-DEPENDENT RHESUS MONKEYS

When evaluated blind, morphine was observed to suppress withdrawal signs in the monkey with an estimate of potency to be about half that of our archival morphine standards.

UM 1312, 792 NIH 9930, 8503 MCV 4261,4002



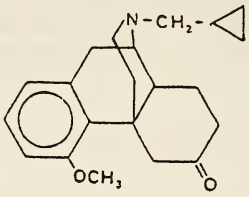
MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 10% @ 20, 40% @ 50, 10% @ 100
Nilsen: 0% @ 20 & 40

Naltrexone hydrochloride

OBSERVATIONS OF MORPHINE-DEPENDENT RHESUS MONKEYS

When evaluated blind, naltrexone was observed to precipitate withdrawal with an estimated potency equal to our archival naltrexone standards.

UM 1313 NIH 9931 MCV 4280



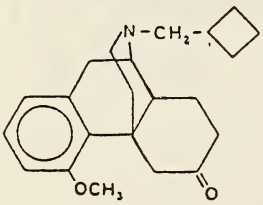
MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 21.7 (17.9-26.3)
Nilsen: 0% @ 10, 40% @ 20

(-)-N-Cyclopropylmethyl-4-methoxymorphinan-6-one

OBSERVATIONS OF MORPHINE-DEPENDENT RHESUS MONKEYS

UM 1313 precipitated withdrawal with a potency of 0.03 times that of naltrexone.

UM 1314 NIH 9932 MCV 4281

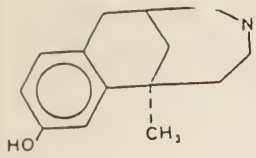


MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 50% @ 20, 60% @ 50
Nilsen: 3.6 (2.5-5.4)

(-)-N-Cyclobutylmethyl-4-methoxymorphinan-6-one hydrochloride

OBSERVATIONS OF MORPHINE-DEPENDENT RHESUS MONKEYS

UM 1314 suppressed withdrawal with a potency about the same as that of morphine.



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 10.1 (7.1-14.4)

(+)-1-Methyl-4-isopentenyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

UM 1315 failed to displace significantly tritiated etorphine up to a concentration of 2×10^{-6} M.

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC50	Maximum Response (%)
Drug alone	4.61×10^{-6} M	48.7
After naltrexone		71
After UM 979		56.6

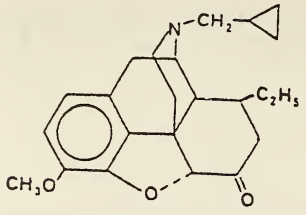
In the presence of naltrexone in a concentration of UM 1315 of 10^{-5} M and greater a 71% inhibition of the twitch resulted. In the presence of UM 979, in concentrations of UM 1315 of 10^{-5} and greater, a 56.5% inhibition of the twitch resulted. EC50's in the presence of the antagonists could not be calculated.

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response (%)
Drug alone	1.51×10^{-6} M	69.5
After naltrexone	2.10×10^{-6} M	58.4
After UM 979	3.12×10^{-6} M	47.1

SUMMARY

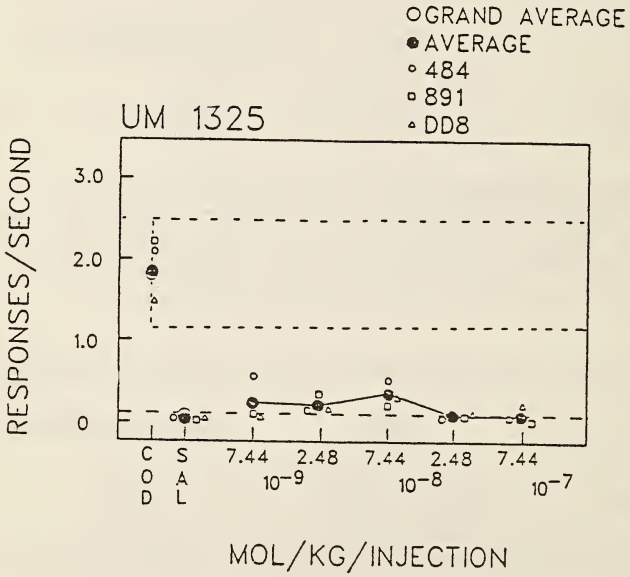
On the smooth muscle preparations UM 1315 appears to have some opiate activity although on both preparations this drug is of extremely low potency. See also the racemate (UM 1308) and (-)-isomer (UM 1278) of this compound.



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 16.8 (10.5-26.9)
Nilsen: 0% @ 20, 50% @ 50 & 100

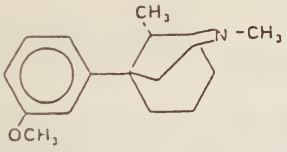
N-Cyclopropylmethyl-8 beta-ethyl-N-nordihydrocodeinone hydrochloride

DRUG SELF-ADMINISTRATION IN RHESUS MONKEYS



Rates of responding maintained by UM 1325 were only slightly higher than those maintained by saline at doses of 7.44×10^{-9}, 2.48×10^{-9} and 7.44×10^{-8} mol/kg/inj.

UM 1327 NIH 9945 MCV 4286



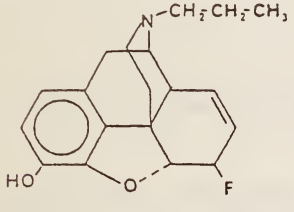
MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 10% @ 20, 50% @ 50 (90% dead @ 100)

(+)-2,9-beta-Dimethyl-5-(m-methoxyphenyl)morphan hydrobromide

OBSERVATIONS OF MORPHINE-DEPENDENT RHESUS MONKEYS

UM 1327 did not reverse withdrawal but rather produced sedation, ptosis and mydriasis at doses of 17.0 and 30.0 mg/kg. The compound did not precipitate withdrawal at a dose of 17.0 mg/kg.

UM 1330 NIH 9939 MCV 4270



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 10% @ 20, 30% @ 50
Nilsen: Inactive @ 100

6,7-Didehydro-4,5 alpha-epoxy-6-fluoro-3-hydroxy-17-n-propylmorphinan

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING (0.5 nM)

EC50 of 66 nM in absence of NaCl
EC50 of 30.8 nM in presence of NaCl
Sodium response ratio = 0.47

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC50	Maximum Response (%)
Drug alone	3.73×10^{-9} M	57.4
After naltrexone	3.44×10^{-7} M	43.0
After UM 979	completely antagonized	

In the presence of both naltrexone and UM 979, UM 1330 increased the baseline tension at concentrations of 3×10^{-5} M and higher.

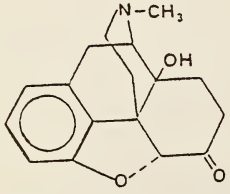
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response (%)
Drug alone	1.42×10^{-9} M	57.9
After naltrexone	2.82×10^{-9} M	46.2
After UM 979	1.15×10^{-8} M	48.6

SUMMARY

UM 1330 has potent narcotic actions on each of the preparations. It has opiate activity upon the isolated ileal preparation which is completely abolished by UM 979 and antagonized by naltrexone. Similarly, it has opiate activity upon the vas deferens preparation which is antagonized only by UM 979. It may, in addition, have antagonist activity as suggested by the findings from the binding assay.

UM 1338 NIH 9957



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 0.46 (0.38-0.54)

(-)-4,5-Epoxy-14-hydroxy-N-methylmorphinan-6-one

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING (0.5 nM)

EC50 of 259 nM in absence of NaCl
EC50 of 492 nM in presence of NaCl
Sodium response ratio = 1.90

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC50	Maximum Response (%)
Drug alone	1.13×10^{-6} M	43.2
After naltrexone		no response
After UM 979	4.49×10^{-6} M	20.2

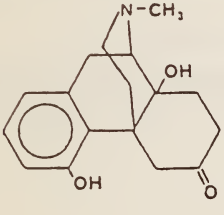
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response (%)
Drug alone	1.79×10^{-6} M	100
After naltrexone	1.27×10^{-5} M	100
After UM 979	5.20×10^{-6} M	100

SUMMARY

UM 1338 had significant opiate action in each of the preparations though it was less potent than morphine in each. Since the compound was reversed by both antagonists on both smooth muscle preparations, it may have morphine-like actions in vivo.

UM 1339 NIH 9958



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 0.57 (0.49-0.67)

(-)-4,14-Dihydroxy-N-methylmorphinan-6-one

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING (0.5 nM)

EC50 of 27.6 nM in absence of NaCl
EC50 of 38.9 nM in presence of NaCl
Sodium response ratio = 1.41

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC50	Maximum Response (%)
Drug alone	1.91×10^{-7} M	51.0
After naltrexone	2.85×10^{-5} M	46.5
After UM 979	1.59×10^{-6} M	46.0

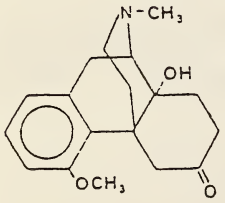
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response (%)
Drug alone	21.7×10^{-7} M	100
After naltrexone	3.42×10^{-6} M	100
After UM 979	1.12×10^{-6} M	100

SUMMARY

Upon each of the preparations, UM 1339 had significant opiate activity, approaching, in some cases, the potency of morphine. It may have morphine-like activity in vivo based on the fact that both antagonists reverse the actions of UM 1339 on both smooth muscle preparations.

UM 1340 NIH 9959 MCV 4305



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 0.16 (0.12-0.21)

(-)-14-Hydroxy-4-methoxy-N-methylmorphinan-6-one

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING (0.5 nM)

EC50 of 70.7 nM in absence of NaCl
EC50 of 101 nM in presence of NaCl
Sodium response ratio = 1.43

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC50	Maximum Response (%)
Drug alone	1.12×10^{-7} M	55.0
After naltrexone		completely blocked
After UM 979	2.66×10^{-6} M	45.5

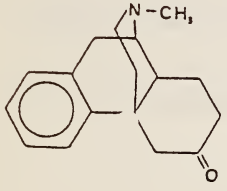
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response (%)
Drug alone	2.53×10^{-7} M	98.0
After naltrexone	1.14×10^{-5} M	96.7
After UM 979	1.10×10^{-6} M	95.7

SUMMARY

UM 1340 had significant opiate actions upon each of the preparations. It was somewhat less potent than morphine, but may share its *in vivo* actions since UM 1340 was antagonized by both antagonists on both smooth muscle preparations.

UM 1344 NIH 9960



MOUSE ANALGESIA, ED50 (mg/kg)

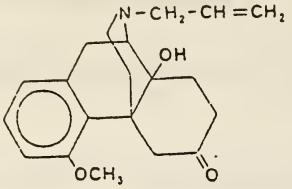
Hot Plate:	0.33 (0.27-0.40)
Nilsen:	0.21 (0.15-0.28)

(-)-N-Methylmorphinan-6-one

OBSERVATIONS OF MORPHINE-DEPENDENT RHESUS MONKEYS

UM 1344 suppressed withdrawal with a potency about ten times that of morphine.

UM 1347 NIH 9975 MCV 4296



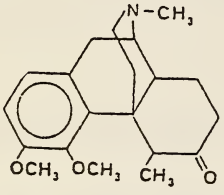
MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 0% @ 20, 20% @ 50

(-)-N-Allyl-14-hydroxy-4-methoxymorphinan-6-one

OBSERVATIONS OF MORPHINE-DEPENDENT RHESUS MONKEYS

UM 1347 precipitated withdrawal with a potency of about one thirtieth that of naloxone.

UM 1381 NIH 10015 MCV 4317



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 0.81 (0.62-1.1)

(-)-3,4-Dimethoxy-5,17-dimethylmorphinan-6-one hydrobromide

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING (0.5 nM)

EC50 of 105 nM in absence of NaCl
EC50 of 116 nM in presence of NaCl
Sodium response ratio = 1.11

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC50	Maximum Response (%)
Drug alone	3.65×10^{-8} M	63.7
After naltrexone	9.06×10^{-6} M	46.6
After UM 979	1.95×10^{-6} M	44.2

In all preparations, concentrations of UM 1381 of 10^{-5} M and higher increased the magnitude of the twitch. No concentration of this drug caused a baseline contraction.

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response (%)
Drug alone	9.50×10^{-8} M	98.9
After naltrexone	2.86×10^{-6} M	100
After UM 979	3.70×10^{-7} M	99.1

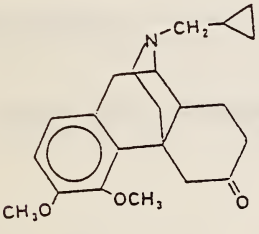
OBSERVATIONS OF MORPHINE-DEPENDENT RHESUS MONKEYS

UM 1381 suppressed withdrawal with a potency of about that of morphine.

SUMMARY

UM 1381 appears to be a morphine-like agonist upon both smooth muscle preparations. These data agree with the previous report that this compound suppresses morphine abstinence completely at doses comparable to morphine.

UM 1384 NIH 10017



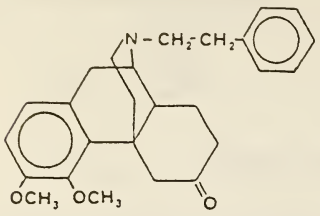
MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 3.9 (2.8-5.5)
Nilsen: 11.1 (6.2-19.6)

(-)-N-Cyclopropylmethyl-3,4-dimethoxymorphinan-6-one hydrobromide

OBSERVATIONS OF MORPHINE-DEPENDENT RHESUS MONKEYS

UM 1384 was without appreciable effects in doses from 1.0 to 10.0 mg/kg. Higher doses were not tested since the supply of the compound was depleted.

UM 1385 NIH 10018



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 0.14 (0.10-0.18)

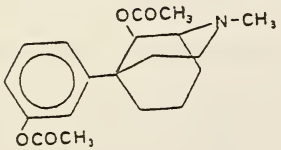
(-)-3,4-Dimethoxy-N-(2-phenethyl)morphinan-6-one hydrobromide

OBSERVATIONS IN NORMAL AND MORPHINE-DEPENDENT RHESUS MONKEYS

UM 1385 reversed withdrawal with a potency comparable to that of morphine. Its effects in normal subjects, except pupil dilation, were reversed by naloxone (1.7 mg/kg, s.c.).

UM 1388 NIH 10021

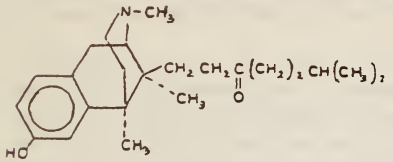
MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 2.0 (1.4-2.8)



9 beta-Acetoxy-2-methyl-5-(m-acetoxyphenyl)morphan hydrobromide

OBSERVATIONS IN MORPHINE-DEPENDENT RHESUS MONKEYS

At doses from 1.0 to 10.0 mg/kg UM 1388 was without effect. Higher doses were not tested as the supply was exhausted.



MOUSE ANALGESIA, ED50 mg/kg)
Hot Plate: 1.1 (0.8-1.3)

1-[2-alpha,6-alpha,11S)-(±)-1-(1,2,3,4,5,6-Hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocin-11-yl)]-6-methyl-3-hepatanone methanesulfonate

PRIMARY DEPENDENCE STUDY

In studies in withdrawn morphine-dependent monkeys conducted at The Medical College of Virginia, this drug neither suppressed nor exacerbated withdrawal. A primary dependence study was terminated prematurely as subjects were unconscious after injections. The present study initially increased dose very slowly in an attempt to allow more tolerance to develop to the sedative effects of the drug.

Subjects. Three rhesus monkeys weighing from 4.4. to 5.5 kg were used. Each monkey lost about 1.0 kg over the 32 days of chronic drug administration.

Dosage Schedule.
The drug was dissolved in water

Day	Dose (mg/kg/6 hr, s.c.)
1	1.0
2	3.0
5	5.6
12	10.0
23	17.0
35	Abrupt withdrawal

Subjects were tested for precipitation of withdrawal with nalorphine on days 15 and 29, and with naloxone on days 18 and 32.

Acute Effects. There were no obvious effects of 1.0 mg/kg. With the increase in dose to 3.0 mg/kg, there was some pupil dilation, scratching, and decreases in activity and eating.

Chronic Effects. Apparent tolerance developed to effects at 3.0 mg/kg by the third day so the dose was increased to 5.6 mg/kg with little increase in effects. Since the subjects were losing weight, that dose was maintained until the 12th day of the study when it was increased to 10.0 mg/kg. At this dose one monkey (FQ-35) was observed to assume peculiar postures with little muscle tone but could be aroused by observers. All three monkeys lost weight at this dose. Additionally, abscesses developed at injection sites. At 17.0 mg/kg a second monkey showed a loss of muscle tone and was

lying on the cage floor. This subject also could be aroused by observers. On the fifth day at 17.0 mg/kg, monkey FQ-35 was found dead one hour after an observation indicating no obvious effects.

Dependence. Nalorphine administered on days 15 and 30 produced very mild, if any, signs of withdrawal. Naloxone had greater effects than nalorphine. Subjects were observed to be lying on their sides, vocalizing, and restless after naloxone administration on day 33. With the abrupt discontinuation of drug administration, only very mild signs of withdrawal were observed in the two surviving monkeys.

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